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Archives of Internal Medicine

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THE PRODUCTION OF BRIGHT'S DISEASE BY FEEDING HIGH PROTEIN DIETS*

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For nearly a century the etiology of Bright's disease has been the subject of much medical thought and investigation. But in spite of this, the clinician is still unable to find a cause for the disease in the great majority of cases seen by him. The present investigation was undertaken with the hope of throwing some additional light on this difficult subject.

The chief business of the kidneys is to rid the organism of the end products of protein metabolism. This task is accomplished to a considerable extent by active secretion on the part of certain portions of the tubular epithelium. These cells will not only remove normal waste, but they will also remove from the blood stream substances which are foreign to it even though they may be severely injured by the poisons passing through them. Thus investigators[1] have shown that when the kidney eliminates such substances as mercury, or the salts of uranium and chromium, a high grade tubular nephritis may be produced; and that the acute tubular injury may be followed by a chronic nephritis.

The substances dealt with by this group of investigators do not play any considerable rôle in the causation of clinical nephritis. But the experiments demonstrate a fact of great importance, namely, that the tubular epithelium may suffer any degree of injury including death as a result of its efforts to remove certain abnormal substances from the blood.

The degree of injury produced by the nephrotoxic substances is largely dependent on their concentration in the blood. Thus mercury in therapeutic doses usually has no detectable effect on the kidney; although when its use is long continued, albumin and casts may appear in the urine. But when swallowed in large amounts in soluble form, acute fatal nephritis may result. Whether mercury will injure the

* From the Department of Internal Medicine, University of Michigan.

1. McNider, W. deB.: J. M. Research **34**:177 (May) 1916.

kidney, is determined not alone by certain qualities inherent in mercury, but also by the quantity of mercury which passes through the kidney in a unit of time.

May this same principle be applied to the nitrogenous bodies habitually secreted by the renal cells? May it not be true that the kidneys can secrete a certain amount of nitrogenous matter for an indefinite period without suffering harm, but that they will be injured if the quantity of some or all of the nitrogenous substances secreted be increased and kept at the higher level for some time?

The experiments which form the substance of this paper were undertaken with the intention of discovering whether nephritis will be produced when the kidneys have been eliminating an unusually large amount of nitrogenous material over a considerable period of time.

To attain this end, rabbits were fed diets abnormally high in protein. The experiments fall naturally into three groups determined by the type of protein used.

Group A includes all those animals whose nitrogen metabolism was increased by means of egg white.

Group B consists of rabbits that lived on a diet high in protein because of the addition of casein.

The animals in group C were fed soy beans.

GROUP A.—THE EGG WHITE EXPERIMENTS

All the animals in this group received egg white, but the diets were of three different sorts, each planned with a different object in view. The group may accordingly be subdivided into three subgroups, 1, 2 and 3.

Subgroup 1.—The preliminary experiments of the investigation fall under this heading. The object was to determine as quickly as possible whether the ingestion of large amounts of protein would produce demonstrable injury of the kidney in a relatively short time.

For this purpose six rabbits were each fed the whites of two hard boiled eggs daily for one week. During this time they received no other food. Thereafter rabbits Nos. 1 and 3 each ate the whites of four or five hard boiled eggs, and, in addition, were each allowed from 25 to 50 gm. of carrots daily. The feeding was continued in this way for thirty days in the case of rabbit No. 1; and for thirty-eight days in the case of rabbit No. 3. Rabbits Nos. 2, 4, 5 and 6, after the first week, ate the whites of from three to four eggs and received no other food. This second period for these four rabbits lasted, respectively, nine, ten, fourteen and twenty days.

The urine of none of these six rabbits contained either albumin or casts, the day preceding the experimental diet. A persistent albumin-

uria developed during the experimental period in the case of each rabbit. It was noted as early as the third day in the urines of rabbits Nos. 1 and 6; and on the fifth day in the urines of rabbits Nos. 2 and 3. Casts were seen in the urines of four of the rabbits, Nos. 1, 2, 3 and 6.

Rabbit No. 5 was found dead on the nineteenth day of the experiment. The remaining rabbits were killed as soon as they refused to eat the hard boiled egg white.

Microscopic examination of the kidneys was made. In every instance cloudy swelling and congestion was seen. Numerous casts were present in the kidneys of each of the rabbits with the exception of No. 6.

What value shall be placed on the data obtained from these rabbits? These data are albuminuria, casts in the urine and numerous casts seen in the microscopic sections of the kidneys, cloudy swelling and congestion. The last two, swelling and congestion, are features which all histologists recognize as variables. They are, in part, at least, related to the preparation of the tissues for microscopic examination. Taken by themselves, in the absence of other signs, they are feeble evidence of renal damage due to high protein diets.

What significance has the albuminuria? Is the albumin in the urine merely white of egg, absorbed as such from the intestine and filtered out of the blood as such by the kidney? It has been clearly demonstrated that this is not the cause of the albuminuria, but that the albumin found in the urine comes from the rabbit itself. The evidence appears in the following two experiments.

EXPERIMENT 1.—Rabbit No. 8, March 1, 1917. The diet has consisted entirely of hard boiled egg white for the past six days. The rabbit has a well marked albuminuria. Ten c.c. of blood are withdrawn from the heart. It is defibrinated by beating and the plasma is obtained by centrifuge. One c.c. of the whole plasma and 1 c.c. of each of the following dilutions, 1:10, 1:20, 1:50, 1:100, are placed in a series of tubes. To each tube 1 c.c. of a 1:1,000 solution of Kaulbaum's egg white is added. The tubes are kept at 38 C. over night. No precipitate is seen in any of the tubes the next morning.

A rabbit whose urine contains albumin consequent to the ingestion of egg white shows no detectable trace of the egg white in his blood.

EXPERIMENT 2.—Rabbit 13, Feb. 12, 1917. The diet has consisted entirely of hard boiled egg white for the preceding ten days. The urine shows a well marked albuminuria. One c.c. of this urine is injected into the peritoneal cavity of each of four guinea-pigs.

Blood is also withdrawn from the heart of this rabbit. It is allowed to clot and the serum is obtained by centrifuge. One c.c. of this serum is injected into the peritoneal cavity of each of four guinea-pigs.

February 24. The guinea-pigs which received the intraperitoneal injection of albuminous urine twelve days ago, are today each given intraperitoneally, 2 c.c. of a 1:100 solution of Kaulbaum's egg white. No reaction is observed.

One-half hour later, two of these same guinea-pigs are given an intravenous injection of normal rabbit's serum. Both showed typical anaphylactic shock.

The group of guinea-pigs which received the intraperitoneal injection of serum obtained from Rabbit 13, twelve days ago, today are each given intravenously 2 c.c. of a 1:100 solution of Kaulbaum's egg white. No reaction is observed. One-half hour later these same guinea-pigs are given an intraperitoneal injection of normal rabbit's serum. Typical anaphylactic shock resulted.

The intraperitoneal injection of the albuminous urine from a rabbit eating egg white, failed to sensitize guinea-pigs to egg white, but did sensitize them to rabbit's serum albumin. The intraperitoneal injection of serum obtained from a rabbit eating egg white failed to sensitize guinea-pigs to egg white, but did sensitize them to rabbit's serum albumin.

The albuminuria produced by feeding egg white may accordingly be accepted as satisfactory evidence of renal injury.

Casts are agglomerations of broken down renal epithelium. They are not found in the urines of normal rabbits. A very few casts may occasionally be found in the sections of supposedly normal rabbit kidneys. Their presence in large numbers in the urines and in the kidneys of the rabbits that received the egg white, is an unquestionable sign of kidney injury.

There is, then, clear evidence that a diet restricted to egg albumin with or without the addition of a small amount of carrot, is capable of quickly causing some renal damage.

Subgroup 2.—These experiments were planned with the object of showing whether recurring periods of excessive protein metabolism would injure the kidneys.

The animals were fed as much hard boiled egg white as they would eat for intervals of about nine days, alternating with periods of stock diet lasting about a week. This type of feeding was continued as long as the rabbits would eat the egg white.

There are four satisfactory experiments, lasting, respectively, four, four and one-half, five and one-half and six and one-half months. Three of the rabbits ate about three egg whites daily. One rabbit (No. 9) ate about five egg whites daily.

This rabbit was found dead at the end of six and one-half months. The microscopic examination of the kidneys revealed cloudy swelling, marked congestion, hemorrhage into the subcapsular space compressing the tufts and many casts. The kidneys of another one of these rabbits (No. 10) showed abnormalities of the same sort, but less well marked.

Both these animals were found dead. The necropsies revealed no important disturbances other than those found in the kidneys. Rabbit No. 9 had, however, lost 600 gm., and rabbit No. 10 lost 900 gm.

during the experimental period. Death may, accordingly, have been caused by inanition.

The two remaining animals of this group were killed. Their kidneys showed no changes which could certainly be attributed to the effect of the diet.

The urines of each of the four rabbits contained albumin during the experimental period.

The ingestion of large amounts of egg white as administered in this subgroup does not cause any serious chronic renal lesions, but evidence of some kidney disturbance has been obtained. No further conclusions are warranted.

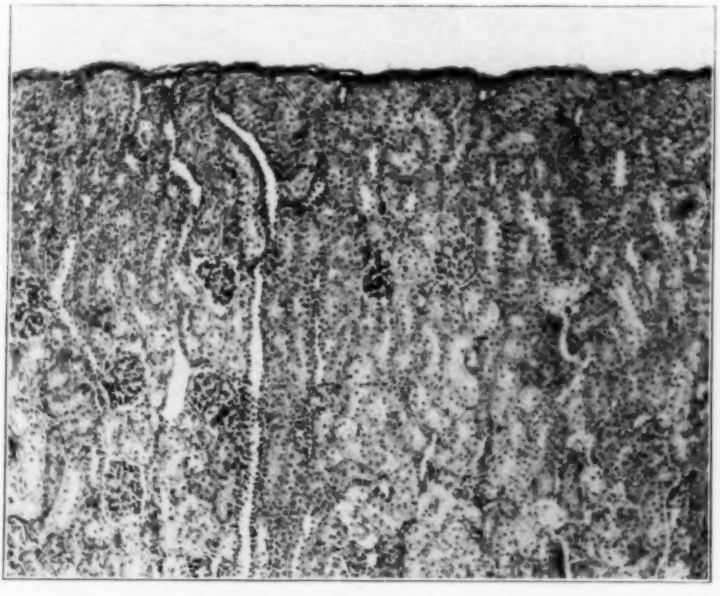

Fig. 1.—Microphotograph of the kidney of a normal rabbit.

Subgroup 3.—All the animals thus far dealt with lost weight while living on the experimental diets. It might be contended that the malnutrition was at least partly responsible for the renal injury. In order to obviate this possible source of error, a third series of rabbits was fed the egg white combined with other food in such a way as to guard against nutritional disturbances.

Each animal received the following mixture daily: three egg whites; 30 gm. of corn meal; sufficient bran (about 25 gm.) to make a stiff paste when the three ingredients were stirred together. The mass was

then transferred to a buttered pan and baked in a hot oven for about twenty minutes. In addition to this, each animal received 25 gm. of bread daily, and some cabbage or a carrot several times a week. This diet furnishes about 230 calories daily. It contains about 17 gm. of protein, about 33 gm. of carbohydrate, and about 2 gm. of fat. One third of the dry weight of the diet is protein.

Three rabbits, Nos. 110, 111 and 113, ate this diet for six months, four months and seven months, respectively. No. 110 maintained its weight, No. 111 gained about 450 gm., and No. 113 gained about 225 gm. The urine of each of the animals showed a marked albuminuria, and many granular and hyaline casts on every examination.

Rabbit No. 110 was killed at the end of six months. It had shown no sign of disease other than the abnormal urine. At necropsy the organs revealed no gross abnormality. Microscopic examination of the kidneys did not disclose any abnormalities which could be attributed to the diet.

Rabbit No. 111, after four months of the diet, began to refuse the egg white mixture and was accordingly killed. The kidneys weighed 21 gm., which is about twice the normal average. On microscopic examination, severe parenchymatous injury was seen. This was especially marked in the convoluted tubules whose epithelium showed granulation, swelling, vacuolization and desquamation. Some nuclei were unstained, others were much swollen. There were many casts in the convoluted and collecting tubules. The glomeruli were somewhat swollen, but there was no exudate in the subcapsular space. Many tufts showed extreme congestion. There was a little increase of young connective tissue in the cortex. Edema and engorgement were marked throughout the section.

Rabbit No. 113 ate the diet containing the whites of three eggs for seven months. During this time he gained 225 gm. and showed no signs of disease other than albuminuria and cylindruria. At the end of this period, the diet was changed so that it contained the whites of five eggs daily. None of the other factors in the ration were altered. The animal ate this latter diet for three months. During this period he gained about 330 gm. and appeared to feel exceptionally well. At the end of these three months he was killed. For seven months he had ingested three egg whites daily and for the next three months he had eaten five egg whites daily.

At necropsy the kidneys were found to weigh 22 gm., which is about twice the normal. The microscopic examination of the kidneys showed a well marked injury of the tubular epithelium, especially severe in the convoluted tubules. Desquamation, vacuolization and irregular disappearance of the parenchymatous cells was widespread.

Casts were numerous. In places, dilatation of tubules was seen. The kidney as a whole showed engorgement and edema. The glomeruli showed no specific injury. There was no fibroblastic increase. The thoracic aorta from the aortic valves to the diaphragm showed very many raised yellow plaques and streaks.

A fourth rabbit, No. 112, was fed the hard boiled egg white as such instead of the mixture of egg white, corn meal and bran. He also ate 50 gm. of bread and a few greens daily. This diet furnished about 180 calories daily. The rabbit took this diet well for three months. During this time he lost 200 gm. Thereafter, for the next

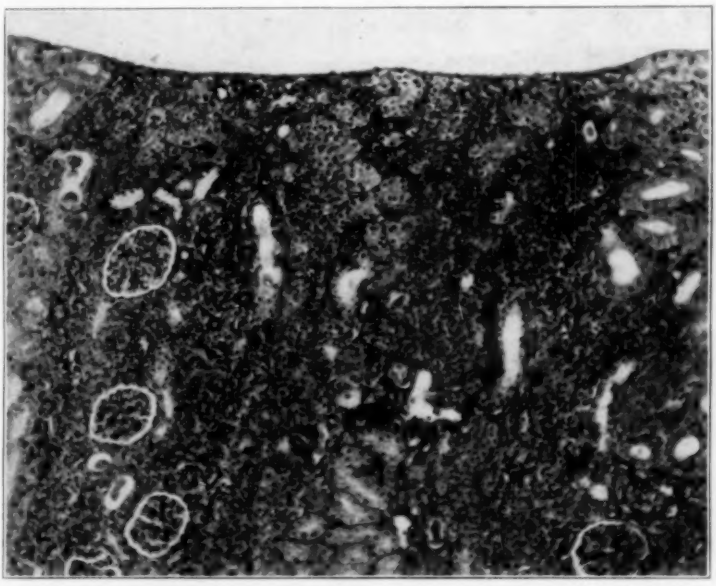

Fig. 2.—Early stage of chronic nephritis produced by the soy bean diet. Note the beginning contraction of the cortex and the pinching off of a group of tubules by connective tissue. Casts are seen.

ten days he ate only the egg white. Two or three days before he was killed he began to show marked weakness. This increased until he became ataxic and unable to hold up his head. He lost 330 gm. during these ten days. He was then killed by a blow on the head. At necropsy a few small areas of pulmonary congestion were found. The kidneys were pale and cloudy. They weighed 15 gm. (average normal is 11.8 gm.). The urine obtained from the bladder contained a large amount of albumin, many granular and hyaline casts, and numerous red blood cells. The microscopic examination of the kidney gave clear

evidence of severe acute injury. Many glomeruli were crowded with red blood cells. Masses of red blood cells and desquamated epithelium were seen in a few subcapsular spaces. The tubular epithelium, and more especially that of the convoluted tubules, showed granulation, much desquamation and marked vacuolization. Red blood cells were seen in the lumen of a few tubules. Some nuclei were swollen, while others were unstained. There were many casts in all parts of the tubules. The collecting tubules were dilated. This experiment presents an example of acute Bright's disease caused by the ingestion of large amounts of protein in the form of egg white.

At first sight it would appear as if the egg white diet had had a greater effect on this rabbit than on any of the three preceding ones which had eaten the same amount of egg white for longer periods. But a consideration of the nitrogen metabolism[2] of these three rabbits shows that such a conclusion would be incorrect. The total urinary nitrogen eliminated during five days was determined for each of these rabbits. The average twenty-four hours' amount for the rabbits that ate the egg white cooked with corn meal and bran was as follows: Rabbit No. 110, 1.2 gm. total nitrogen; rabbit No. 111, 1.5 gm. total nitrogen; rabbit No. 113, 1.2 gm. total nitrogen while eating the mixture containing three egg whites, 2.3 gm. total nitrogen while eating the mixture containinng five egg whites; rabbit 112, 2.2 gm. total nitrogen. Obviously, the mixture of egg white with corn meal and bran resulted in a very poor absorption of the digestion products of the egg white. But when plain egg white was fed the absorption was excellent, and adequately explains the much more acute injury to the kidney observed in rabbit No. 112.

These data for the nitrogen metabolism of the four rabbits in this subgroup have a further significance. It will be noted that rabbit No. 110, whose twenty-four hours urinary nitrogen was only 1.2 gm., showed no renal changes which could be recognized by the microscope. The absorption of nitrogen from the diet was so poor in this instance as to result in only a slight increase over the normal nitrogen metabolism. The average total twenty-four hours urinary nitrogen in one group of controls was 0.8 gm.; in a second group it was 1.0 gm. Rabbit No. 111, whose absorption was better, 1.5 gm. total nitrogen, showed a subacute nephritis, but was able to gain weight and appeared to feel well up to the time when he was killed four months from the beginning of the experiment. Rabbit No. 113, whose absorption was only 1.2 gm. while he was eating a mixture containing the egg whites, gave no evidence of disease except albumin and casts during the seven

2. A full discussion of the procedure used for determining the urinary nitrogen will be found in the discussion accompanying Table 2, page 375.

months of this diet. The change in his diet which caused him to eat five egg whites daily for the next three months, resulted in a nitrogen absorption of 2.3 gm. daily. He continued to gain weight and to give the outward appearance of health during this second period. But in spite of the steady gain in weight, the autopsy revealed a well marked subacute parenchymatous nephritis.

The data obtained from these four rabbits in Subgroup 3, demonstrate that the renal lesions observed were not a part of a nutritional

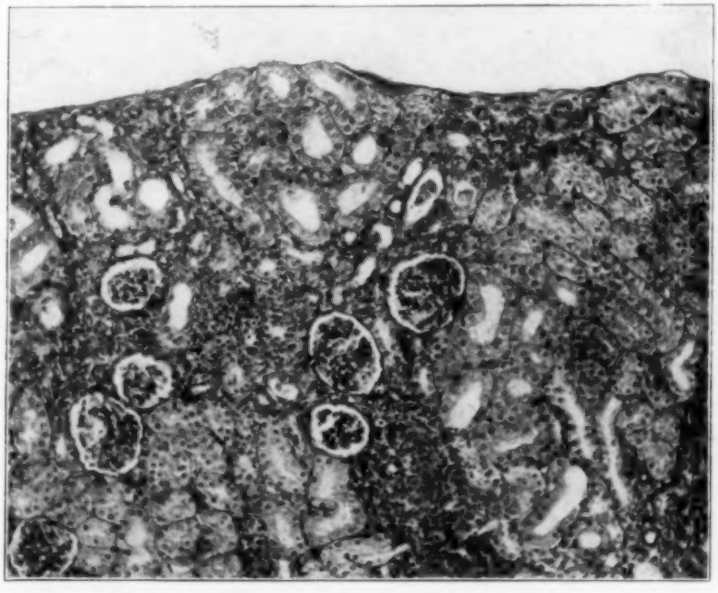

Fig. 3.—A later stage of the soy bean nephritis showing more marked contraction, atrophy of some glomeruli, slight thickening of Bowman's capsule and casts. A broad band of connective tissue occupies the central portion of the field.

disturbance, but were, in fact, the direct result of the injection of egg white.

The information obtained from the various types of experiments with egg white may be summed up by the following statements: (1) When rabbits eat several egg whites daily, evidence of renal injury is very quickly and constantly noted. (2) When rabbits absorb the digestion products of egg white in sufficient quantity for a considerable time, a well marked acute or subacute nephritis may result.

GROUP B.—CASEIN EXPERIMENTS

In order to decide whether the nephritis observed in the preceding group of experiments was the result of the prolonged secretion by the kidney of an excessive amount of one or more of the nitrogenous bodies which, in lesser amounts, are normal constituents of the blood; or whether it might possibly have been caused by some nephrotoxic substance peculiar to egg white, it was necessary to determine whether nephritis would follow the prolonged ingestion of some other protein in excessive amounts.

Casein was chosen for this purpose. The diet was prepared by placing 25 c.c. of milk, 20 c.c. of water and 20 gm. of scraped carrot together in a pan over a hot water bath. When the mixture was warm, the casein and about 1 gm. of sodium bicarbonate was added. The whole was stirred. The gas evolved produced a porous mass which, when cool, somewhat resembled a "baking powder biscuit." Four rabbits were fed 30 gm. of casein daily in this way. Two rabbits received fifteen grams daily. In addition to this the animals received from 25 to 50 gm. of bread daily and a handful of greens about once a week.

The four rabbits which ate 30 gm. of casein daily, were killed at the end of three weeks, ten weeks, four months and eleven months.

The rabbit which was allowed to live only three weeks on the diet, was found acutely ill one morning, and for this reason the experiment was ended. The kidneys weighed 22 gm., or 7.5 gm. per kilogram. (The average weight of the kidneys of eight normal rabbits was 11.8 gm., or 4.9 gm. per kilogram.) On microscopic examination the kidney showed very marked edema and engorgement. There were numerous red blood cells scattered through the subcapsular spaces and the lumina of the tubules. Very many casts were seen. The other organs were normal. The type of renal disturbance found strongly suggests that the symptoms had been caused by acute nephritis.

The second rabbit had seemed to be ill for some days prior to his death. He was killed after he had been eating 30 gm. of casein daily for ten weeks. The kidneys weighed 20 gm.; and, on microscopic examination, showed moderate parenchymatous injury, casts and congestion.

The third rabbit, killed after four months of the diet, showed changes similar to those found in the preceding one, but they were much more pronounced. The kidneys weighed 21 gm.; and, on microscopic examination, revealed marked congestion, severe parenchymatous injury, very many casts and beginning fibroblastic increase.

The fourth rabbit that ate 30 gm. of casein daily was killed at the end of eleven months. The urine contained no albumin before the

casein diet was started, but did give positive tests for albumin thereafter. The kidneys weighed 16 gm., but gave no other evidence of injury due to the diet. Evidently, the high protein diet had either had less effect on the kidneys of this rabbit than upon those of the three preceding animals, or else this fourth rabbit had recovered from a nephritis such as was observed in the others at a much earlier stage of the diet. No choice between these two alternatives is possible.

Two other rabbits ate 15 gm. of casein daily for one year. Their urines showed no albumin before the diet was started. During the course of the experiment the slightest trace of albumin was often noted,

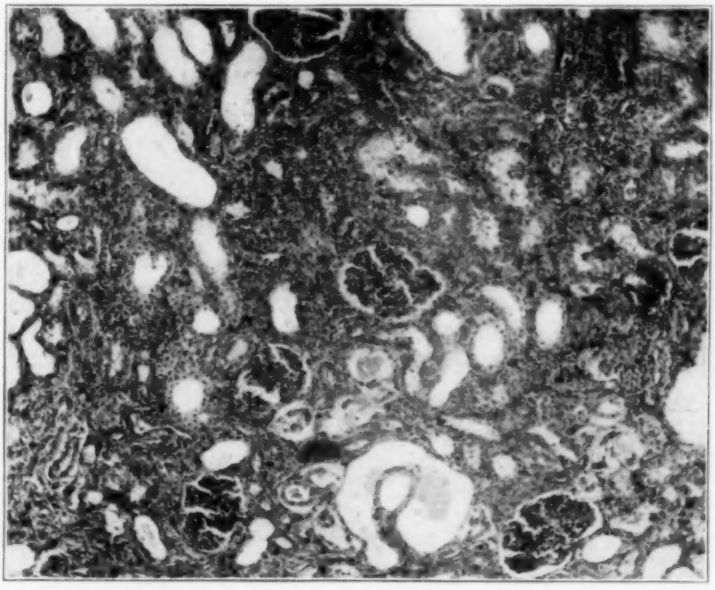

Fig. 4.—A still later stage of the soy bean nephritis showing marked injury of the epithelium of the convoluted tubules. Many convoluted tubules are lined by a flat epithelium; others have entirely lost the epithelial lining. Many tubules are widely dilated. There are many casts. Bowman's capsule shows more thickening. A patchy increase of connective tissue involving most of the field is seen.

but only once were a few casts seen. The kidneys weighed 13.5 gm. and 14.5 gm., respectively. Microscopic examination did not show any abnormalities.

The outcome of the experiments with casein is this: When the nitrogenous metabolism is increased by means of casein, rabbits suffer no renal injury from eating 15 gm. of casein daily, even though this

amount of casein causes the nitrogen metabolism to be about double the normal. But when the daily intake of casein is 30 gm., and the nitrogen metabolism is about three times the normal, a well marked deleterious effect on the kidney was produced in three rabbits out of four.[3]

GROUP C.—SOY BEAN EXPERIMENT

Even though there can be little doubt that the kidney lesions thus far described bear a causal relation to the large amount of protein in the diet, nevertheless it was felt that the evidence would be strengthened if similar results should be obtained by feeding a third type of protein.

For this purpose soy beans were used as the sole food. The soy bean was chosen for a number of reasons: (1) Rabbits habitually eat vegetable protein. A renal injury occurring in herbivora as a result of the ingestion of a large amount of vegetable protein would have more significance than if it had been produced by means of an animal protein. (2) It was to be expected as the result of the studies of Osborne and Mendel,[4] and of Daniels and Nichols,[5] that animals could live on the soy bean[6] for many months without acquiring nutri-

3. The necropsies of the three rabbits whose casein feeding had lasted for a year, revealed an unexpected lesion of great interest. The thoracic aorta in each case was the seat of a well marked arteriosclerotic process. The inner surface of the aorta presented many raised yellow plaques and streaks. The lesion was most extensive at the very beginning of the aorta and included the aortic valves. It gradually became less marked as one passed down the aorta and ended before the diaphragm was reached. None of the other large vessels were involved. The microscopic appearance of the lesion was described by Dr. C. V. Weller as follows: "Rabbit 58. Aorta. Hemalum and eosin and Van Gieson's stains. The intima is thickened irregularly through the presence of elevated plaques, many of which are three to four times as thick as the normal aortic wall. These elevated patches in most cases involve only the intima. In a few instances the innermost lamellae of the media are included. The elevated patches show a proliferation of the intima, increase in the elastic fibers and large areas of secondary fatty degeneration and liquefaction necrosis, accompanied by marked formation of cholesterin. The picture is that of an advanced intimal atherosclerosis in varying stages up to and including secondary atheromatous change with cholesterin formation. The greater part of the media and the adventitia are negative."

This disease of the aorta was found only in the three rabbits that had eaten the casein diet for a year and in the one rabbit (No. 113) of the egg white group that had eaten the egg albumin for ten months. Further study is required to determine whether arteriosclerosis may be regularly caused by the prolonged ingestion of high protein diet.

4. Osborne, T. B., and Mendel, L.: J. Biol. Chem. **32**:369 (Dec.) 1917.

5. Daniels, A. L., and Nichols, N. B.: J. Biol. Chem. **32**:91 (Oct.) 1917.

6. Bulletin No. 28, Office Experiment Stations, Washington, D. C., states the composition of the soy bean as follows: water, 5.5 per cent.; protein from 36 to 43 per cent.; fat, 17 per cent.; ash, ?; carbohydrate (by difference), 34.5 per cent.

tional disturbances. (3) The soy bean is very rich in protein. The beans used by us contained 37.8 per cent. of protein. If the rabbits ate enough of the beans to maintain their weight, they would of necessity also eat very much more protein than was their habit.

Twenty-six rabbits were placed in a large pen consisting of three compartments. The dividing walls were made of wire netting. Some of the rabbits were full grown. The remainder were about six months old and about three fourths grown. The adults were all put in the first compartment. Six of the partly grown rabbits were kept in the second compartment. The remainder of the young rabbits were placed

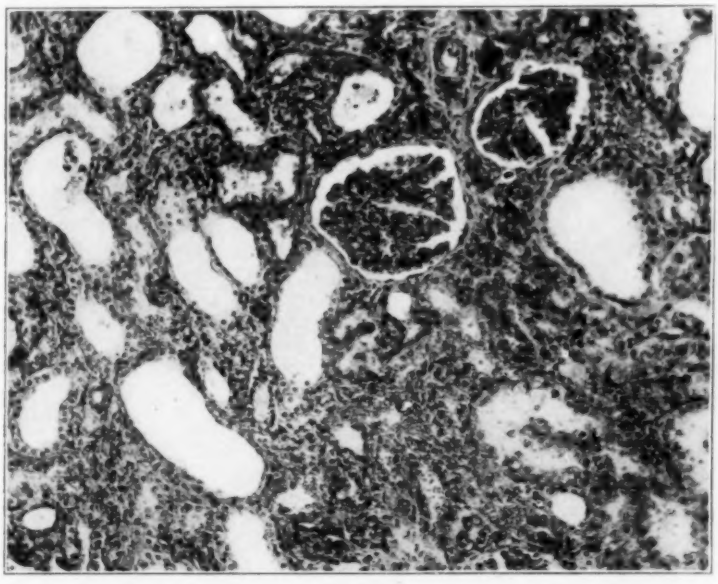

Fig. 5.—A higher magnification of the same field as Figure 4. Note especially the extreme atrophy and dilatation of the tubules.

in the third division of the pen. The six rabbits in the second compartment served as controls. They were fed hay, bread, corn cake, cabbage and other greens. The other two groups in the pen, consisting of twenty rabbits, lived on soy beans and water. All of the rabbits were exposed to the same conditions, except as regards diet. If at the end of the experiment any consistent difference between the kidneys of the control rabbits and of the soy bean groups should be found, this difference would have to be attributed to differences in diet.

The average individual weight of the control rabbits after seven months residence in the pen was 2,415 gm. The partly grown rabbits

averaged 2,179 gm. at the beginning of the soy bean diet. Three months later their average weight was 2,497 gm., an average individual gain of 318 gm. The average weight of the adults at the beginning of the soy bean diet was 2,382 gm. Three months later they weighed, on the average, 2,780 gm. At the end of another three months these animals averaged 2,892 gm. It is evident from a consideration of the above weights that the soy bean, when fed as the only source of food, is not alone adequate for maintenance, but also for growth.

The control rabbits were killed at the end of seven months. Neither the gross nor the microscopic examination of their kidneys revealed any abnormalities.

Of the twenty rabbits that were fed soy beans, five were killed at the end of two months. The kidneys of four of these animals showed no changes. But the kidneys of the fifth rabbit showed degeneration of the epithelium of the convoluted tubules and very many casts.

Fifteen rabbits lived on an exclusive diet of soy beans for from four and one-half months to twelve months. Eight of these fifteen rabbits died. Microscopic examination of the kidneys showed acute or chronic nephritis in every instance. In addition to this, two of the animals had pneumonia and one a bacterial endocarditis. In five of the eight animals that died while on the soy bean diet, no cause of death other than Bright's disease could be found. Seven of the fifteen rabbits were killed by a blow on the head after they had lived on the soy bean diet for from four and one half to twelve months. The microscopic examination of these kidneys showed, with one exception, subacute and chronic nephritis. The kidneys of one rabbit, killed at the end of five months, showed only slight injury of the tubular epithelium.

The following protocols and the microphotographs will illustrate the type of kidney lesion which develops in the rabbit as the result of a diet restricted to soy beans.

RABBIT 90.—Nov. 19, 1917: This is one of the young rabbits. He was about three-fourths grown at the beginning of the experiment. April 1, 1918: He was found dead this morning. He had eaten nothing but soy beans for four and one-half months. He weighs 1,590 gm. Necropsy: All organs except the kidneys appear to be normal. The bladder urine contains albumin and many hyaline casts. The heart weighs 7 gm. The kidneys weigh 12 gm. The capsule strips easily, leaving a smooth surface which presents a peppered appearance. Microscopic examination[7] of the kidney: "Patchy degenerative nephritis, shown by cloudy swelling, atrophy, dilatation of tubules and obliteration of some convoluted tubules by connective tissue. Bowman's capsule is thickened in many instances. There is some thickening of the arterial walls. The glomeruli show varying stages of atrophy, congestion of capillaries and degeneration of epithelium. Van Gieson's stain shows marked increase in

7. I am grateful to Dr. A. S. Warthin for this and other descriptions of the microscopic anatomy of the kidneys.

connective tissue, especially marked in the labyrinths but extending into the medullary rays. There is very little cellular infiltration in these areas. Many granular and hyaline casts are seen."

RABBIT 98.—Nov. 5, 1917: Soy bien diet started.

June 25, 1918: After seven and one-half months of the diet the rabbit weighs 3,120 gm. Nov. 5, 1918: The rabbit has eaten nothing but soy beans for one year. It weighs 2,725 gm. Blood was withdrawn from the heart today. It contained 123 mg. of incoagulable nitrogen per 100 c.c., and 128 mg. of urea per 100 c.c. The urine shows a trace of albumin and a few coarsely granular casts.

The animal is now placed on a diet of greens, oats and bread. Nov. 17, 1918: It weighs 2,610 gm. November 18: The total incoagulable nitrogen of the blood is 89 mg. per 100 c.c.; the urea is 52 mg. per 100 c.c. December 2, 1918: The animal weighs 2,440 gm. The total incoagulable nitrogen of the blood is 123 mg. per 100 c.c.; the blood urea is 60 mg. per 100 c.c. The urine shows a trace of albumin but no casts.

A consideration of the figures for incoagulable nitrogen and blood urea shows that both were about twice the normal for rabbits, four weeks after this animal had been placed on a normal diet. The nitrogen retention is evidence of a serious disturbance in renal function. It is also worthy of special note that the animal lost 285 gm. during the last four weeks of his life in spite of the fact that he was receiving a normal diet. The continuous loss of weight under these conditions, indicates that the rabbit was seriously ill.

Dec. 3, 1918: Necropsy: All organs but the kidneys appear to be normal. They weigh 15 gm. The capsule strips easily, leaving a finely granular surface. Microscopic examination shows a well marked irregular increase in connective tissue. Just beneath the capsule, fairly large patches of connective tissue have caused contraction in these areas. The connective tissue extends in irregular bands through the cortex deep into the medulla. Many of Bowman's capsules are much thickened. Many glomeruli show atrophy, and a few, marked scarring. The convoluted tubules are dilated and lined with a flattened epithelium whose nuclei are picnotic. Desquamation of the tubular epithelium is seen in some places. There are many casts throughout the section.

The protocols and the photographs of the kidneys make it clear that the nephritis produced by the soy bean closely resembles the chronic nephritis commonly found in human subjects — the secondarily contracted kidney of the pathologists. The lesion is not the result of arteriosclerosis, for the arteries are not diseased. Nor are we dealing with a primary glomerulonephritis. Judging by the constancy and severity of the damage to the epithelium of the convoluted tubules, the firm impression is gained that the offending substance has its primary and chief deleterious effect upon the epithelium of these tubules and that this slowly progressing injury of the convoluted tubular epithelium is accompanied by an overgrowth of the connective tissue.

The soy bean nephritis causes a marked interference with renal function. There is an early and persistent retention of blood urea. Table 1 shows the blood urea readings in normal animals and in animals that had lived on soy beans for (1) seven weeks and for (2) six months. The normal animals ate hay, oats and bread. All the animals were fasted for twenty-four hours before drawing the blood

This precaution was taken in order to avoid an error in favor of the nephritis rabbits. Since these animals were eating abnormally large amounts of protein, their blood urea might be abnormally high during the digestive period. But the undamaged kidney would eliminate any excess of blood urea from that source during the twenty-four hours' fast.

TABLE 1.—Blood Urea in Normal and in Soy Bean Rabbits

Normals		Rabbits Living on Soy Beans			
Hay, Oats, Bread		Seven Weeks		Six Months	
Number	Urea per 100 C.c.	Number	Urea per 100 C.c.	Number	Urea per 100 C.c.
A	42 mg.	33	83 mg.	—	—
B	33 mg.	34	90 mg.	—	—
C	17 mg.	35	84 mg.	35	176 mg.
D	36 mg.	36	96 mg.	36	118 mg.
E	29 mg.	37	98 mg.	37	78 mg.
F	33 mg.	38	98 mg.	38	87 mg.
Average	31 mg.	Average	100 mg.	Average	115 mg.

The experiments described above leave no doubt that a well marked chronic nephritis is produced in rabbits when the diet is restricted to soy beans. Evidence has been presented to show that the renal lesion is not the outcome of a lack of any essential food constituent. Nor can the lesion be attributed to an hypothetical nephrotoxic substance in the bean. For the habitual use of the soy bean by the Japanese and Chinese as food, and the excellent results obtained by Osborne and Mendel,[4] and by Daniels and Nichols[5] when the bean was the sole source of protein in the diet, make it highly improbable that the bean contains any poisonous substance which could so regularly and seriously damage the kidney of the rabbit. The only tenable explanation, in the light of the results obtained with egg white and casein, is one which relates the nephritis observed in each group of experiments, to the common factor, namely, the high protein content of the diet.

NITROGEN METABOLISM

Having now shown that nephritis may be produced in rabbits by feeding high protein diets, it is of interest to compare the nitrogen metabolism of such rabbits with that of rabbits eating a normal diet. To that end the following plan was used.

The rabbits used as normals were taken from a stock cage and placed in metabolism cages. They were fed oats and carrots, and allowed to eat as much of the weighed amount offered as they chose. The first twenty-four-hour specimen of urine was discarded. All the urine voided during the next five days was saved and measured.

Enough strong HCl was placed in the receptacles to make the urine acid. The urine was acidified to prevent loss of urea. It had been found previously that the urea in the alkaline rabbit urine gradually breaks down. The total amount of each food eaten during the five day period was determined, and the approximate amount of protein eaten was calculated from Atwater and Bryant's tables. The urines were analyzed for total nitrogen, urea nitrogen and ammonia nitrogen. All calculations were reduced to a twenty-four hour period. The normal data were obtained from six rabbits. Exactly the same procedure was followed with the three rabbits of Subgroup 3, eating egg white, three rabbits on casein diets and four of the rabbits living on soy beans.

TABLE 2.—PROTEIN EATEN, PROTEIN ABSORBED AND NITROGEN EXCRETED IN URINE

	Rabbit No.	Protein Eaten, Gm.	Protein* Absorbed, Gm.	Urine			
				Total N, Gm.	Urea N, Gm.	Urea, Gm.	Amount, C.c.
Controls	—	8.5	5.2	0.85	0.64	1.37	105
	—	11.2	5.7	0.91	0.50	1.07	109
	—	11.4	4.2	0.67	0.53	1.13	74
	—	8.0	4.5	0.72	0.59	1.26	107
	—	13.0	4.8	0.78	0.61	1.31	62
	—	9.7	5.7	0.91	0.89	1.90	90
	Average	10.3	5.0	0.81	0.63	1.34	91
Egg white	110	15.0	7.9	1.21	1.12	2.40	87
	111	15.0	9.2	1.48	1.44	3.08	120
	112	15.0	13.9	2.23	2.05	4.40	182
	113	15.0	7.4	1.19	1.17	2.50	155
	113	25.0	14.3	2.24	1.80	3.90	120
	Average	—	—	—	—	—	—
Casein	57	15.0	11.5	1.54	1.06	3.65	70
	58	15.0	11.9	1.91	1.87	4.0	93
	61	30.0	14.8	2.38	2.25	4.80	220
	Average	—	—	—	—	—	—
Soy Beans	38	10.7	8.2	1.32	1.08	2.31	114
	92	26.6	14.0	2.24	2.05	4.39	202
	96	19.0	12.9	2.07	1.83	3.92	111
	96	8.4	8.2	1.32	1.15	2.46	60
	Average	17.7	10.8	1.74	1.53	3.27	122

* This figure is obtained by multiplying the total urinary nitrogen by 6.25.

Table 2 shows that when rabbits are living on what may be considered a normal diet, they eat by choice about 10 gm. of protein daily; but that they absorb only about 5 gm., or half of the protein eaten. The same relation holds in regard to the mixture of egg white, corn meal and bran. Rabbits which ate this mixture containing about 15 gm. of protein absorbed about 8 gm. of protein. When, however, plain, hard boiled egg white was fed, nearly all of it was absorbed. A correspondingly greater effect on the kidney was noted. The absorption of the digestion products of casein was

very good in the case of the rabbits that received 15 gm. of casein daily. They had a nitrogen metabolism of more than twice the normal. It will be seen from the table that the ingestion of soy beans by the four rabbits tested was quite variable. In order to get a more reliable figure for the average daily consumption of the beans, the amount eaten by eight different rabbits during seven-day periods was determined. The consumption was measured for thirty such periods. The resulting average was 40 gm. of beans eaten daily by each rabbit, with a variation from 22 to 80 gm. The beans used by us contain 37.8 per cent. of protein, hence the animals were eating 15 gm. of protein daily. This is somewhat less than the ingestion by the four rabbits during the test period. However, the individual averages of these four rabbits determined in the case of the first one from seven periods, for the second, third and fourth ones from four periods each, gave the following average intakes: 13.9 gm., 18.1 gm., 17.0 gm., 12.0 gm. The average is 15 gm., which is the general average. The figure found in the table for average protein absorption is probably also a little high, but cannot be far from correct. Accordingly, it may be stated that the protein metabolism of rabbits whose sole food is the soy bean, is about twice the normal.

When these figures for protein absorption from the various diets are compared with each other, it is seen that a chronic nephritis is produced when soy beans are eaten in sufficient quantity to double the total nitrogen metabolism. But casein and egg white must be fed in sufficient amounts to treble the total nitrogen in order to injure the kidney seriously; and furthermore, the injury from both casein and egg white tends to be acute rather than chronic. Apparently, the kidney is not injured by the secretion of that portion of the total nitrogen which is formed in amounts corresponding to the quantity of protein absorbed, for if that were the case, the injury to the kidney would be expected to be proportionate to the amount of protein absorbed, regardless of the source; and urea, which is the quantitatively important end-product of all protein metabolism, would be expected to damage the kidney in proportion to the amount secreted by it. But a comparison of the urea figures for soy bean rabbits with the average urea output of three rabbits eating casein, shows that the soy bean produced nephritis in rabbits that were secreting 3.3 gm. of urea daily, whereas the casein food failed to produce nephritis in rabbits whose urea averaged 4.1 gm. daily. This question was investigated further by feeding 5 gm. of urea daily to three rabbits that were eating an otherwise normal diet. The rabbits ate the urea for two, three and nine months, respectively. Analysis of the urine for urea showed that they were eliminating a little more than twice the normal amount. The

urines occasionally contained the slightest trace of albumin, but never any casts; and microscopic examination of the kidneys failed to show any abnormalities which could be attributed to the urea. It may accordingly be definitely stated that the renal lesion produced by feeding high protein diets is not caused by the passage of too much urea through the kidney.

It would appear rather that the kidney injury was related to those digestion products of protein which vary both quantitatively and qualitatively with the type of protein eaten. In this connection, one thinks of the amino acids. They form a constant constituent of the urine, and the quantity of amino acid nitrogen found in the urine is proportionate to the protein metabolism. On the other hand, individual members of the group are found in large amounts in some proteins and are nearly absent from others. Whether the amino acids are responsible for the nephritis can only be determined by studying their effect on the kidney. At present, no data which will throw any light on this question are available.

SUMMARY

In the majority of cases of chronic Bright's disease the cause of the nephritis cannot be discovered. This investigation has been undertaken with the intention of determining whether the elimination of abnormally large amounts of nitrogenous material by the kidney will cause nephritis. To this end, high protein diets have been fed to rabbits. The following results were obtained:

1. Renal injury was very quickly and constantly noted in rabbits that ate several egg whites daily.

2. Prolonged egg white feeding caused acute and subacute nephritis.

3. When the nitrogenous metabolism was increased by means of casein, rabbits suffered no demonstrable renal injury from eating 15 gm. of casein daily; but when the daily intake of casein was 30 gm., and the nitrogen metabolism was about three times normal, a well marked deleterious effect upon the kidney was produced.

4. Rabbits that lived on soy beans for months regularly acquired chronic nephritis and frequently died of it. The nitrogen metabolism from this diet was about twice the normal.

5. The renal lesion produced by feeding high protein diets was not caused by the passage of too much urea through the kidney.

The data suggest that the kidney injury is related to those digestion products of protein which vary both quantitatively and qualitatively with the type of protein eaten.

CUTANEOUS REACTION AND DESENSITIZATION IN QUININ IDIOSYNCRASY*

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The purpose of this communication is to add two new cases of idiosyncrasy to quinin to the long list of such instances encountered in the literature, with an allusion to a skin reaction and attempts at densensitization.

CASE 1.—G. V. W., male, chief yeoman, aged 22 years, was admitted to the U. S. Naval Hospital, Washington, D. C., as a case of influenza. His illness pursued a typical course and in two weeks he had recovered completely. During the latter days of his convalescence elixir of iron, quinin and strychnin were prescribed for him in 4 mil doses. Within fifteen minutes after the first dose was administered, the eyes began to smart and itch. There was some photophobia and lacrimation. Soon the face, neck, chest and hands became a "lobster red" color, which rapidly became a generalized erythema. This was attended by an intense pruritus. There was a certain degree of headache, puffiness of the eyelids and muscae volitantes, but no vertigo nor tinnitus aurium were noticed. Some dyspnea and epigastric burning were encountered. The erythema and pruritus completely disappeared in two and one-half hours.

On questioning the patient, it was learned that during childhood quinin was frequently taken for coryzal attacks on which occasions no untoward symptoms occurred. Not until eight years ago was any reaction from this drug noticed, when an attack, similar to the one just described, followed the ingestion of approximately 0.2 gm. of quinin. The second attack occurred one year later, when a similar dose was taken. From this time on until two years ago, the patient on several occasions took tablets containing, in addition to other ingredients, 0.065 gm. of quinin. No ill effects were noticed from these until October, 1917, when, after taking one tablet, a syndrome was caused, characterized by erythema, pruritus, edema, headache, vertigo, tinnitus, muscae volitantes, dyspnea, nausea and vomiting. Since 1917 the patient has not taken quinin in any form until his admission to the Naval Hospital.

He says he can eat eggs, cucumbers, strawberries, tomatoes, buckwheat and all types of sea food with impunity. He never had hay fever or horse asthma. Typhoid or smallpox vaccine did not occasion any undue reaction.

His past, family and personal history reveal no noteworthy features. Physical examination is negative.

CASE 2.—Captain S., U. S. Marine Corps, male, aged 28 years, married was admitted to the U. S. Naval Hospital, Washington, D. C., complaining of tenderness, weakness, loss of weight and stiffness in the legs and thighs There was no cough and repeated physical examinations and thoracic roentgenograms failed to reveal any tuberculous process. The patient had returned

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on sick leave from eighteen months duty in San Domingo, where, since early in March, 1918, he had experienced three definite attacks of benign tertian malaria. The first two attacks were three months apart—in March and June, 1918. They were clinically typical and responded readily to 1 gm. of quinin sulphate, three times a day. On both occasions absolutely no untoward effects were caused by the quinin, nor had the patient ever had cinchonism prior to this time, despite the fact that he had taken 1 gm. of quinin a day as a prophylactic ten years previously while on an engineering expedition in South America. In December, 1918, a third attack of malaria was experienced. As in the previous two attacks, he had distinct chills, forty-eight hours apart, and the *plasmodium vivax* was found in the blood smear. Quinin therapy was instituted. The first dose, 1 gm. of quinin sulphate, produced no ill effects. The second dose of the same size, given a few hours later, caused a blotchy, diffuse rash, generalized pruritus, headache, tinnitus aurium, muscae volitantes, photophobia, lacrimation, dyspnea, epigastric flushes of heat, nausea and diarrhea. This attack persisted for several hours. Therefore the drug was discontinued for two days and then given subcutaneously, once a day. Each injection was attended by a syndrome similar to the first though milder. Having apparently recovered from malaria, the patient returned to this country.

Except for an attack of amebic dysentery in 1913, his health has always been good. Has never had any hay fever, horse asthma nor any reactions to the various fruits, vegetables, sea food or drugs other than quinin.

It would appear from an analysis of these cases that the hypersensitiveness to quinin was acquired. In neither case could a similar familial tendency be elicitetd. The clinical manifestations were extremely suggestive of cinchonism, and it was found that neither individual reacted with any of the other common drugs where idiosyncrasies are known to occur. Furthermore, it was found that the tolerance of Case 1 was somewhat less than 0.03 gm. when given by mouth, and that of Case 2 was about 0.25 gm. when given by mouth or intravenously in a 5 per cent. solution. Both men failed to react clinically with the other alkaloids of cinchona, whereas the various salts of quinin produced a reaction in sufficient dosages.

After the method of Boerner,[1] skin reactions were tried in both cases. Two superficial abrasions were made with a sterile needle on the flexor surface of the forearm, about 3 inches apart, after the parts were cleansed with 95 per cent. ethyl alcohol and dried. To one was applied quinin bisulphate (1:10) while the other was left untouched, functioning as a control. We were able to confirm Boerner's findings in that the scarification to which the quinin antigen had been applied showed a marked reaction in both men, while the control merely exhibited the results of the traumatism. The reactions began with an itching, smarting or burning sensation from four to five minutes after application. This was quickly followed by an area of edema on either side of the needle scratch. This edematous area was, as a rule, irregular in outline and reached its height in from fifteen or twenty minutes to one hour. It was surrounded by a bright red halo of erythema, which

1. Boerner, F., Jr.: J. A. M. A. **68**:907 (March 24) 1917.

varied from 3 to 5 cm. in diameter. An identical reaction could be produced by the use of the chlorhydrosulphate or dihydrochlorid of quinin in 1:20 dilutions. Control tests, as shown in Figure 1, of salicylic acid (10 per cent.), caffein citrate (10 per cent.), potassium iodid (saturated solution), atropin sulphate (0.5 per cent.) and epinephrin (1:1,000) failed to provoke analogous reactions in either patient.

Later, additional controls were made, using cinchonin sulphate, and cinchonidin sulphate as antigens. No reactions were encountered with these alkaloids of cinchona, whereas the quinin yielded the usual intense response.

Twelve individuals were selected who were known not to be hypersensitive to the drug. All were given as much as 2 gm. of quinin sulphate a day without manifesting any discomfiture. The cutaneous tests in all these men were negative. As Boerner indicated, there is reason to believe that the reaction is specific to those who are hypersensitive to quinin, and, also, it has been found that these two patients failed to respond to other idiosyncrasy-producing drugs, even to certain other alkaloids of cinchona.

An attempt was now made to desensitize the patients to quinin. The procedure described by Heran and Saint Girons[2] gave brilliant results in Case 1, while the tolerance in Case 2 was increased from 0.25 to 0.7 gm. The method, briefly, consisted in giving by mouth a "desensitizing dose" of 0.005 gm. with 0.5 gm. of sodium bicarbonate. In one hour and thirty minutes, 0.1 gm. of quinin bisulphate and 0.5 gm. of sodium bicarbonate were ingested in cachets. The "desensitizing dose" remained constant each day, while, in the second dose, the amount of quinin was increased 0.1 gm. each day. The quantity of sodium bicarbonate remained the same. Only one dose was given in any one day. It was found that, except for the "desensitizing dose" on the first day, Case 1 showed no untoward symptoms. At the end of the eleventh day, 2 gm. were being taken without any disagreeable symptoms. Case 2 did not respond so readily, and it was necessary to discontinue the procedure when 0.7 gm. was taken on account of a diarrhea and some visual disturbances. It is of interest to note that the degree of intensity of the skin reaction was in inverse ratio to the amount of quinin ingested without ill effect. In Case 1 the cutaneous reaction gradually became less marked, until on the tenth day it completely disappeared. The reaction in Case 2 became gradually less distinct until 0.7 gm. was given, but when the toxic symptoms manifested themselves there was efflorescence which simulated in intensity that encountered in the initial tests.

2. Heran and St. Girons: Montpellier med. **39**:21, 669, 1917.

Two other methods of desensitization were instituted in Case 2. One was the administration of quinin bisulphate, by mouth, in increasing doses once a day. The initial dose was 0.03 gm. and it was increased by as much each day. The other method consisted in giving a "desensitizing dose" of 0.01 gm. quinin chlorhydrosulphate in 5 mils of sterile water, intravenously, and, after from thirty to forty-five minutes, giving a second dose starting with 0.2 gm. of the same drug and increasing 0.1 gm. a day. By both methods 0.7 gm. could be given with safety, but symptoms appeared if larger quantities were administered.

We are not prepared to offer a theory as to the nature of these reactions in terms of anaphylaxis or allergy. Many investigators, adherent to either the humoral or cellular theories of anaphylaxis, agree that a protein must be associated with its provocation, while others maintain that proteins are not necessary. If it were true that a protein must be involved in the production of anaphylaxis, idiosyncrasies and skin reactions to various alkaloids, which are not proteins, would seek explanation on some other basis. Several authors, notably Zieler[3] and Pöhlmann,[4] have placed these phenomena in the realm of intoxications rather than manifestations of anaphylaxis, basing their conclusions, for the most part, on the inability to produce passive sensitization in animals with the sera of hypersensitive persons. On the other hand, Klaussner[5] and Bruck[6] report passive sensitization in guinea-pigs by injecting the sera of individuals with idiosyncrasies to drugs.

Hans Meyer has evolved a theory that there is an alteration in the calcium content of the tissues, while, on the other hand, Pepper and Krumbhaar[7] deny that there is a deficiency in calcium metabolism in edema and urticaria. Hunt[8] and Lewis[9] have shown that a certain percentage of cases of poison susceptibility can be influenced by diet.

Kolmer,[10] who has had a vast experience with skin reactions, refers to them as "anaphylactic or pseudo-anaphylactic." He states that there is not sufficient data at hand to prove that the mechanism of the local or skin anaphylactic reaction is identical with that of the general or fatal reaction following intravenous injections. He, as well as Longcope,[11] admits that examples of drug anaphylaxis, unless such drugs contain protein substances, offer certain difficulties as to explanation,

3. Zieler: München. med. Wchnschr. **59**:401, 1641, 1912.
4. Pöhlmann: München. med. Wchnschr. **61**:543, 1914.
5. Klaussner: München. med. Wchnschr. **57**:1451, 1983, 1910; **58**:138, 1911.
6. Bruck: Berl. klin. Wchnschr. **47**:517, 1928, 1910.
7. Pepper, W., and Krumbhaar, E. B.: J. Infect. Dis. **14**:476, 1917.
8. Hunt, R.: U. S. P. H. and M. H. S. Hyg. Lab. Bull. **69**: 1910.
9. Lewis, J. H.: J. A. M. A. **72**:329 (Feb. 1) 1919.
10. Kolmer, J. A.: Infection, Immunity and Spec. Ther., 1917, p. 617; Bull. Johns Hopkins Hosp. **28**:163 (May) 1917.
11. Longscope, W. T.: Am. J. M. Sc. **152**:6125 (Nov.) 1916.

but maintains that a drug may be capable of sensitizing body cells in the same manner, as in the "indirect anaphylaxis" of Richet, or that a new protein compound is formed in the patient's serum to which he may be "actively sensitized."

SUMMARY

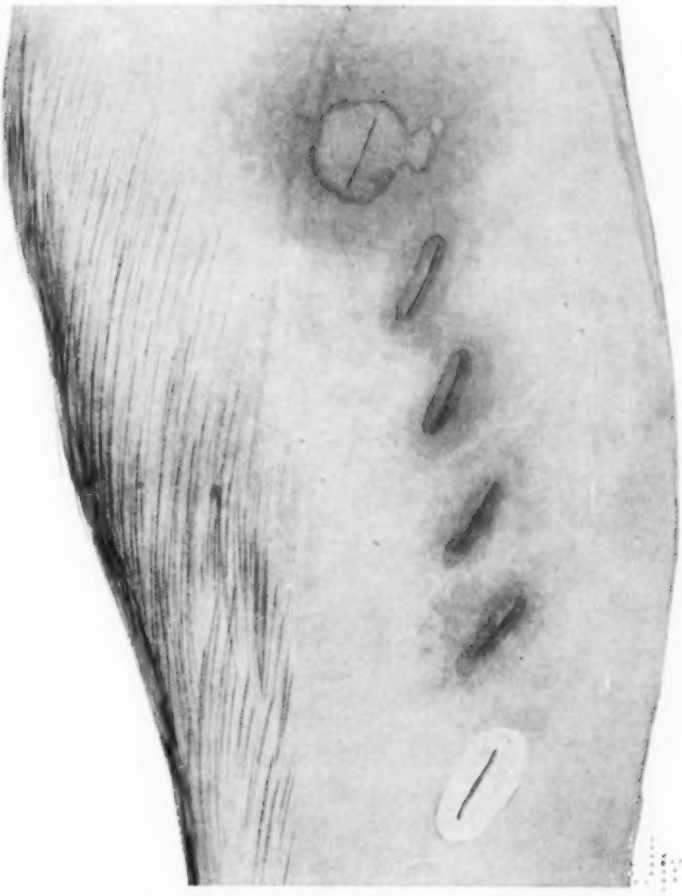
In the two cases of idiosyncrasy to quinin, the skin test descsibed by Boerner has been found a good index to hypersensitiveness.

2. These cases reacted to various salts of quinin only, failing to respond to cinchonin, cinchonidin, salicylic acid, caffein citrate, potassium iodid, atropin sulphate and epinephrin.

3. A method of desensitization described by Heran and Saint Girons proved efficacious in one case and increased the tolerance in another.

4. The intensity of the cutaneous reaction was found to be in inverse ratio to the degree of desensitization obtained.[12]

12. Lutz, W.: Cor.-Bl. f. schweiz. Aerzte **47**:1601 (Dec. 1) 1917. Sollmann, T.: J. Pharmacol & Exper. Therap. **9**:309 (March) 1917. Strickler, A.: New York M. J. **104**:198 (July 29) 1916. Zinnser: Infection and Resistance, 1919, p. 410.



From above downward the drugs employed were quinin bisulphate (1:10), salicylic acid (10 per cent.), caffein citrate (10 per cent.), potassium iodid (saturated solution), atropin sulphate (0.5 per cent.) and epinephrin (1:1,000).

Illustrating Article by John J. O'Malley, M.D., and DeWayne G. Richey, M.D.,
Archives of Internal Medicine, October, 1919

PROTOZOOLOGIC AND CLINICAL STUDIES ON THE TREATMENT OF PROTOZOAL DYSENTERY WITH BENZYL BENZOATE

I. A PRELIMINARY REPORT ON EIGHT CASES OF ENDAMEBIC DYSENTERY AND ONE CASE OF BACILLARY DYSENTERY TREATED AT THE PHILIPPINE GENERAL HOSPITAL

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MANILA, P. I.

WITH AN ADDENDUM BY

M. A. ASUZANO, M.D.
BAGUIO, P. I.

Several months ago the attention of the senior author was attracted by the investigation of the action of the benzyl esters carried out by Macht[1] at Johns Hopkins University. The pharmacologic action of the two esters, benzyl acetate and benzyl benzoate, which formed the subject of Macht's investigations, suggested, as Macht has pointed out, their application to the treatment of the protozoal dysenteries, especially in view of the nontoxic nature of these infections. In his paper, Macht cited a case in which benzyl benzoate was applied, with apparent success, in the treatment of a case of endamebiasis of fifteen years' standing which had been contracted in the Philippine Islands, and this determined us to make a trial of the drug in the wards of the Philippine General Hospital.

Some benzyl benzoate was prepared locally for us and it was found to exert no untoward effects on guinea-pigs when injected pure in moderately heavy doses; but when it was tried out on one or two patients it was found to contain some traces of an impurity which set up a slight degree of gastric irritation and we decided to discontinue its use. Later, we used some of a small batch of the drug prepared at the Bureau of Science, Manila, in three cases. One patient of the three complained of slight nausea; the others took it without experiencing any ill effects.

The senior author entered into correspondence with Dr. Macht, who very kindly had the manufacturers, Messrs Hynson, Westcott & Dunning, of Baltimore, send us a small supply of the pharmaceutically prepared miscible benzyl benzoate, put up in 20 per cent. alcoholic solution. This was used in all of the cases hereinafter recorded except

1. Macht, David I.: A Pharmacological and Therapeutic Study of Some Benzyl Esters, J. Pharmacol & Exper. Therap. **11**:419 (July) 1918.

in the three already mentioned, and in no instance did we observe any untoward effects on the gastrointestinal or urinary tracts, or, indeed, ill effects of any nature.

In starting the work it must be confessed that we had to cope with the prevailing opinion held by many tropical workers, that it is unwise to check the diarrhea in dysentery except through the medium of the specific treatment employed. We are inclined to disapprove of the administration of bismuth or opium in such cases, but we think the objection lies mainly in the treatment of bacillary dysentery which we have only briefly touched on in this series. The protozoal dysenteries are nontoxic, that is to say, so far as the protozoal infection is concerned, and we consider that there is much less danger in checking the diarrhea caused by them than is to be feared from checking the diarrhea of bacillary dysentery, especially through the use of opium. The checking of the diarrhea through the slowing down of peristalsis has been a striking feature of the results we have observed in this series, and in no case has this action been attended by other than good results.

It is our intention to continue these studies. We shall not limit our work to the treatment of endamebiasis, but, as opportunity offers, shall try it in the treatment of the dysenteries caused by *Balantidium coli* and the flagellated protozoa found in the human intestinal tract. The supply of the drug obtained through Dr. Macht was limited, and much of it was saved for use in the treatment of a case of lymphatic leukemia by the same author, in collaboration with Dr. Asuzano, the results of which will be published elsewhere. Our principal object in connection with this short series, was to accustom ourselves to the action of the drug and to outline plans for a more systematic study of its action in the future. In our next paper we shall give a fuller treatment of the action of the drug on the parasites. This paper is mainly a clinical study.

Ten cases were selected in the wards of the hospital and subjected to the treatment to be described. Of these cases, eight were endamebic uncomplicated by infection with *Bacillus dysenteriæ,* one was bacteriologically positive for *Bacillus dysenteriae* (Shiga) and showed no evidence of coexisting endamebic infection. The other case was discovered to be one of miliary tuberculosis, in a late stage, with diarrhea. The patient was dropped from the series and died a few days later. To these must be added two cases of endamebiasis treated at the Baguio Hospital by Dr. Asuzano, whose report appears as an addendum to this paper. All the patients left the hospital either free from dysenteric symptoms of any kind, or so markedly improved that they refused to stay longer. How many of these cases represent cures, in

the generally accepted sense, can only be determined by future developments. In no case, except in one of Dr. Asuzano's cases (Case 2), has it been possible to keep the patient under observation. We are reluctant to pronounce a case of endamebiasis "cured" until the stools have been free from trophozoites or cysts for a period of at least thirty days. We incline to the opinion that this period is none too long. Endamebiasis is essentially a chronic disease, as is malaria, and is prone to exhibit surprises to the clinician and microscopist, not dissimilar to syphilis.

Another factor that must be borne in mind in the event that any of these patients applies in the future for treatment of endamebiasis, is that all of them, with the exception of Dr. Asuzano's cases, were individuals belonging to the poorer classes whose ideas of hygiene and sanitation are not even elementary. Unless cases can be controlled with almost military rigor, as may sometimes be done with the inmates of a prison, the worker in the tropics is always uncertain in such cases whether he is dealing with a recrudescence of the original attack or a fresh infection.

In each case we made every effort to secure a correct diagnosis, and we believe that we have been successful in every one of the cases we are presenting. The microscope was used in the determination of the type or types of parasites present and to discover the nature of the cellular exudate carried in the stool. This was checked up, in each instance, where there was the slightest suspicion of a coexisting bacillary infection, by bacteriologic examination by Dr. Walfrido de Leon of the department of pathology and bacteriology, to whom the authors extend their thanks. The customary weight was also placed on the clinical manifestations.

Microscopic diagnosis requires careful interpretation by an experienced worker, but we believe that, in the main, it is more to be relied on than bacteriologic diagnosis under the methods and technic now available to the bacteriologist. We base a diagnosis of endamebiasis only on the finding of the trophozoites of *Endameba dysenterica* as shown by amebae containing ingested erythrocytes, or the discovery of the characteristc quadrinucleated cysts. The character of the exudate carries much weight with us, however. If the cellular elements of the stool are scanty in amount, contain few leukocytes of the polymorphonuclear type and exhibit cells that show evidence of having undergone proteolytic digestion, we suspect endamebiasis, but suspend judgment until we have identified the ameba.

We have found the bacteriologic examination of stools for *Bacillus dysenteriae* a weak reed to lean on. A negative report carries no weight with us. It is our practice to insist that the stool be carried to the

bacteriologist immediately after it has been passed, for experience has shown us, as it has shown many other workers, that delay in the examination of the stools lessens the chances of detecting the bacillus.

The character of the exudate is of value as has been shown by Wenyon and O'Connor,[2] Willmore and Shearman[3] and others, although many of the distinctive features they have pointed out have been known to tropical workers for a long time. We regard as suspicious of bacillary dysentery a stool that is rich in cellular exudate, mostly of a polymorphonuclear nature, one that is strongly indicative of an acute inflammatory process and of toxic necrosis.

Stools of the latter type are often found to contain *Endameba dysenterica*. In such cases it is customary to regard the condition as probably one of mixed bacillary and endamebic infection. Infections of this type are common in the Philippine Islands. But, as time goes on, the conviction is growing on us that such stools are not necessarily indicative of mixed bacillary and endamebic dysentery. We are not in entire accord with authors who hold that endamebic dysentery does not become complicated by invasion of the amebic ulcers in the intestinal wall by bacteria other than *Bacillus dysenteriae* with consequent evidence, in the stools, of an acute inflammatory process, and we lean strongly towards the statement made by Cowan and Miller[4] that they doubt the existence of pure endamebic infection as they are skeptical of the existence of chronic bacillary dysentery. It is this factor that seems to us to inject an element of doubt into the otherwise apparently reliable method of cytodiagnosis as employed in the dysenteries.

In addition to the direct examination of samples taken from different parts of the stools, it is our practice to concentrate the stools after a modification of the method of Cropper and Row.[5] This is done when the patient is admitted to determine the extent of associated parasitism present and again when the patient is discharged from the hospital in order to detect the cysts of *Endameba dysenterica*. Table 1 shows the result of the examination in each case on admission.

As a routine measure, all our patients received aperient sulphates. In some instances enemas of potassium permanganate were given to clear out the bowel when the stools were formed. Ipecacuanha, when

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2. Wenyon, C. M., and O'Conner, F. W.: An Inquiry Into Some Problems Affecting the Spread and Incidence of Protozoal Infections of British Troops and Natives in Egypt, etc., J. Roy. Army Med. Corps **28**:151, 1917.

3. Willmore, J. Graham, and Shearman, Cyril H.: On the Differential Diagnosis of the Dysenteries, Lancet **2**:200 (Aug. 17) 1918.

4. Cowan, John M., and Miller, Hugh: Dysentery: a Clinical Study, J. Roy. Army Med. Corps **31**:277, 295, 1918.

5. Cropper, J. W., and Row, R. W. Harold: A Method of Concentrating Endamoeba Cysts in Stools, Lancet **1**:179 (Feb. 3) 1917.

administered, was given in the form of salol coated pills. The dose on each of three successive nights was 180 cg. In acute cases we give 4 cg. of emetin hydrochlorid daily hypodermically. When the acute symptoms subside we reduce the dose to 2 cg. daily. In very severe cases one may employ the combination of ipecac, emetin and benzyl benzoate.

Pending diagnosis, it is our practice, in fulminating dysentery, to administer serum at once. Because of the acute and rapid course that severe bacillary dysentery runs we deem it to the best interests of the patient to give the serum liberally without waiting for the laboratory report. It can do no harm, and may do a great deal of good, for it is the experience of one of us (P. T. L.) that the serum treatment achieves its best results when applied early in the attack. We are cautious in the application of emetin in undetermined dysentery because of its mischievous effects on the heart that may be impaired in bacillary dysentery.

MICROSCOPIC FINDINGS ON ADMISSION

Case No.	Endameoba dysenterica	Trichomonas intestinalis	Spirochaeta eurygyrata	Ankylostoma duodenale	Trichuris trichiura	Bacillus dysenteriae
67452	+	..	..	+	+	..
67528	+	..	+	..	..	..
67798	..	..	..	+	..	+
67888	+	..	+	..	+	..
68117	+	..	..	+	+	..
68143	+	+	..	+	+	..
68374	+	..	..	+	+	..
68213	+	+	..	..	+	..
68529	+	+	+	+	+	..
Total	8	3	3	7	7	1

The benzyl benzoate we administered in a small amount of cold water three times a day after meals. The doses employed by us varied from 20 to 30 drops of the 20 per cent. alcoholic solution. It will be noted that Dr. Asuzano employed doses of 10 drops only. Notwithstanding this he seems to have secured results which, in the main, seem to be about as good as ours. In our next series we shall endeavor to determine the minimum effective dose as well as the effects of doses even higher than we have employed.

The protocols of our cases are as follows:

REPORT OF CASES

CASE 67452.—Male, 21 years of age, admitted to the hospital February 5. On admission the stool showed a scanty cellular exudate containing traces of mucus, erythrocytes and a few leukocytes. It was positive for *Endameba dysenterica, Trichuris trichiura* and *ancylostoma duodenale.*

The case presented an acute exacerbation of a chronic endamebiasis of about three months' standing, the original attack having occurred in Novem-

ber, 1918. It lasted about one week. The present attack began three days before admission and was not at first accompanied by severe abdominal pain or tenesmus, but during the early part of his stay in the hospital the patient began to complain of both.

As this was not a case of marked severity, it was determined to treat it with benzyl benzoate alone. On the first night after treatment was started the patient slept well. The treatment was started on February 7, with a dose of 20 drops, three times a day. On the following day the abdominal pain and tenesmus were greatly diminished and the patient passed only two stools. The stools were becoming feculent. February 9, the pain and tenesmus had completely disappeared and the stools were practically normal in consistence. The patient was discharged free from dysenteric symptoms on February 16. His stools had averaged one a day since February 9.

This was undoubtedly a mild case. The stools were becoming formed on February 8, seven days after the onset of the attack. Under the benzyl benzoate treatment the patient showed almost immediate improvement which continued uninteruptedly to the day of his discharge.

CASE 67528.—Male, 35 years of age, admitted to the hospital February 8. The stool contained a rather abundant cellular exudate, blood and mucus. The stool was positive for *Endameba dysenterica* and *Spirochaeta eurygyrata*. Bacteriologic examination was negative for *Bacillus dysenteriae*. Nevertheless, the character of the stool was such as to make us strongly suspect bacillary as well as entamebic involvement.

Clinically, the case presented a moderately severe type. The patient had just recovered from an attack of influenza complicated with bronchopneumonia. Six days before admission to the hospital he felt a growing sense of heaviness in the abdomen accompanied by tympanism. This lasted two days. During the following four days the bowel movements became more frequent (ten or more during the twenty-four hours). The movements were accompanied by tenesmus. They were mainly mucoid with a little blood.

On admission, the patient was having four to six movements during the day and from fifteen to twenty at night. The griping and tenesmus had become very severe. The colon was palpable and tender. The patient was very weak and unable to sleep. He was immediately given 20 c.c. of antidysenteric serum intramuscularly and was started on benzyl benzoate, 20 drops three times a day. The following day the bowel movements were diminished to four in the twenty-four hours. The night of February 10, the patient slept well. The pain and tenesmus were greatly diminished and the patient passed but two stools. February 11, there was a slight return of the abdominal pain and tenesmus, but both completely disappeared on the following day when the patient was able to be up and around the ward. The stools were well formed by this time and February 16 the patient left for home free from dysenteric symptoms.

It should be noted that this patient received only one dose of antidysenteric serum and that further treatment was carried out with benzyl benzoate alone. In view of this, it is questionable if the patient had a coexisting infection with *Bacillus dysenteriae*. The cellular exudate in the stool was, however, strongly suggestive of a concomitant bacterial infection of some kind.

CASE 67888.—Male, 35 years of age, admitted to the hospital February 23. The stool contained blood, pus and mucus. There were numerous active *Endamoeba dysenterica* and Charcot-Leyden crystals. Other parasites present were *Trichuris trichiura*, and *Spirochaeta eurygyrata*. Bacteriologic examination for *Bacillus dysenteriae* was negative on two occasions.

Notwithstanding the presence of pus we are convinced that this was a case of frank endamebiasis of a rather severe type. The patient had been suffering from the disease in a rather mild form, for about one month previous. On the day of admission the stools, which had been averaging about twenty in the twenty-four hours, became more frequent. They were scanty, mucoid and streaked with blood. There was marked tenesmus and abdominal pain. The patient was weak and unable to sleep at night.

Immediately after admission the patient was started on antidysenteric serum, 20 c.c. intramuscularly, every four hours. There was no improvement in his condition and February 25 he was started on 25 drops of benzyl benzoate, three times a day. The following day the patient passed only three stools as against nine the day before. There was a marked lessening of the abdominal pain and tenesmus and the patient said he felt much better in every way. The improvement continued, although on the following day the endamebae seemed more numerous in the stools. March 2, all pain and discomfort had disappeared and the stools were formed. March 5, there was complete absence of trophozoites and the concentrated stool failed to yield any cysts. The patient was discharged March 6.

Case 68117.—Male, 55 years of age, was admitted to the hospital March 4. The stool contained much blood, but the cellular exudate was not abundant. *Endamoeba dysenterica* was found as were *Ancylostoma duodenale* and *Trichuris trichiura*.

This case was of interest because of the complete absence of abdominal pain or tenesmus and we deemed it a favorable one on which to observe the effects of benzyl benzoate on peristalsis. The patient said he had suffered from dysentery for twenty-three years, so that the disease may be said to have been thoroughly established. The present attack started February 26, with profuse diarrhea, but with the discharge of neither blood nor mucus. Since the second day of the attack he had experienced difficulty in urination, the urine coming away drop by drop. This condition cleared up later.

On the day of admission the passing of stools was almost constant. The nights of March 5 and 6, ipecacuanha treatment was administered. March 6, benzyl benzoate was started, 30 drops, three times a day. That night the patient slept well for the first time since entering the hospital.

March 8, the general condition of the patient was greatly improved. The effect on peristalsis was very marked for the patient was almost constipated. Later, the stools fell to an average of one a day. The patient was feeling quite well March 11—so well that he insisted on leaving the hospital. His stool was still dysenteric and contained numerous active *Endamoeba dysenterica*. This patient promised to return for treatment on his next attack, which we assured him was probably not far distant.

Case 68143.—Male, 17 years of age, was admitted to the hospital March 5. The stool contained little cellular exudate, but was laden with erythrocytes and Charcot-Leyden crystals. *Endamoeba dysenterica* was found. Other parasites present were *Trichomonas intestinalis, Ancylostoma duodenale* and *Trichuris trichiura*.

On admission the patient complained of abdominal pain and frequent bowel movements containing blood and mucus. The symptoms had developed eight days prior to admission. The patient was able to walk and did not seem particularly sick. There was no palpable mass in the abdomen, but there was slight tenderness on pressure over the ascending colon. The stools were mucoid and streaked with blood and the patient was passing them at the rate of ten to twelve in the twenty-four hours. Defecation was accompanied by pain and tenesmus. Pending diagnosis the patient had received 40 c.c. of antidysenteric serum intramuscularly on the night of admission.

March 7, the administration of benzyl benzoate, 30 drops, three times a day was started. There was little if any relief from the symptoms the following day, but the patient said he felt much better. March 9 he showed a distinct

Improvement. The tenesmus had diminished in intensity and where the stools had the day before been passed at very frequent intervals, there were only twelve stools in the twenty-four hours. March 11, abdominal pain and tenesmus had disappeared completely and there were only three stools passed that day.

The stools had now become quite normal, and as there was no discomfort of any kind present, the benzyl benzoate was discontinued. Against our strongly expressed advice the patient insisted on leaving the hospital the following day. Unfortunately, his stool could not be obtained for examination before his departure. He was advised to return later for examination, but so far he has failed to put in an appearance. It may be said, however, that the last time his stool was examined microscopically (March 8) neither *Endamoeba* nor *Trichomonas* was found and the stool had lost most of its dysenteric character.

Treatment of this case was carried out wholly with benzyl benzoate, neither ipecacuanha nor its derivatives having been administered.

CASE 68374.—Female, 18 years of age, was admitted to the hospital March 15. The patient's stool contained much mucus and active trophozoites of *Endamoeba dysenterica*. Other parasites present were *Ancylostoma duodenale* and *Trichuris trichiura*.

This case presented a rather severe exacerbation of a chronic endamebiasis dating from 1915. The patient began to exhibit dysenteric symptoms with frequent bowel movements of a bloody and mucoid character, abdominal pain and tenesmus.

March 17, the patient was placed on benzyl benzoate (locally made), 20 drops, three times a day. Two days later the pain and tenesmus had disappeared completely and on that day the patient's bowels moved only once. March 20, the patient failed to move her bowels, and as it was not desired to produce constipation, the benzyl benzoate was withdrawn and the patient was placed on a tonic of iron, quinin and strychnin and Fowler's solution of arsenic. Up to the time of her discharge, April 14, no trophozoites or cysts of *Endamoeba dysenterica* could be found in the stools and the patient was gaining strength every day. She had shown no dysenteric symptoms since March 19. In other words, this patient received benzyl benzoate for three days only and yet apparently was completely cured of the attack. It should be noted in connection with this case that the patient received no anidysenteric treatment whatever, except the benzyl benzoate.

CASE 68529.—Male, 55 years of age, was admitted to the hospital March 21. Examination of the stool on admission showed the presence of active trophozoites of *Endamoeba dysenterica, Trichomonas intestinalis* and *Spirochaeta eurygyrata* and the ova of *Ancylostoma duodenale* and *Trichuris trichiura*. The helminthal infections were particularly heavy. By this, it will be seen that the patient was quite extensively parasitized, but such instances of multiple parasitism are not sufficiently rare in the Philippine Islands to excite comment when they do occur. The stool also contained a little pus and mucus.

This was an old chronic case with an acute exacerbation of great severity. The patient had been suffering intermittently from abdominal pains of a vague character since 1908. He would have periodic attacks which lasted about two days and then subsided. It was apparently one of the fairly frequent instances where a chronic or subacute condition has dragged along for a period of years to finally reach a climax in a severe acute attack. The patient was asthenic and emaciated and although the colon was not palpable, there was marked tenderness at the hepatic flexure. The present attack started ten days previous to admission.

The patient was having very frequent bowel movements accompanied by much pain and tenesmus at the time of admission. He was put on ipecac and emetin. For four successive days he received 4 cg. of emetin hydrochlorid hypodermically and on three nights following he received 180 cg. of ipecac each night. The stools diminished in number, but were still passed frequently

and on some days as many as fourteen in twenty-four hours. He gained somewhat in strength, but the pain and tenesmus were undiminished.

At this time the patient was started on the benzyl benzoate (locally made), 20 drops, three times a day. The following day he passed only two stools, but there was no lessening of the pain and tenesmus. The next day following, the pain and tenesmus disappeared completely and the patient had only one bowel movement. The improvement in his general condition was very marked. From that time on the patient never passed more than two stools during the twenty-four hours.

On the fourth day of the administration of the benzyl benzoate the patient began to complain of nausea and the drug was withdrawn with complete disappearance of the trouble. This is the only instance where we observed the slightest ill effects that could be attributed to the benzyl benzoate and it should be noted that the drug administered in his case had been locally prepared and was not the imported pharmaceutical preparation.

During the period when the patient was receiving ipecac and emetin, he was very sick and his condition was at one time extremely unfavorable in outlook. It was found necessary on several occasions to administer camphorated oil and hypodermoclysis. After the benzyl benzoate was withdrawn he received no further antidysenteric treatment until April 12, when a few cysts of *Entamoeba dysenterica* were found in his stool. He was placed on ipecac again for one night and the cysts were absent at the last examination of his stool before he was discharged, April 14. The stool, as in a previous case cited in this paper, was also free from *Trichomonas* but we attach no importance to this because these parasites frequently disappear from the feces for days at a time when the patient is undergoing no treatment whatever, only to reappear later. We doubt the efficacy of any drug which acts through the circulation against lumen dwelling parasites such as *Trichomonas*, unless the drug is eliminated in considerable volume into the lumen at the site of parasitism.

This case afforded an excellent basis for comparison between the effects of ipecacuanha and its alkaloids and benzyl benzoate, for the patient made no real substantial gain until the latter drug was started.

Case 68213.—Male, 26 years of age, was admitted to the hospital March 9. The microscopic examination of the stool showed the presence of slight cellular exudate, erythrocytes and numerous Charcot-Leyden crystals. Numerous active trophozoites of *Endamoeba dysenterica* were found and there were heavy infections with *Trichomonas intestinalis* and *Trichuris trichiura*. An interesting feature of the *Trichomonas* infection was furnished by the numerous agglomerations of these flagellates seen as the slide was studied.

The case was one of comparatively long standing, the patient complaining that he had suffered from dysenteric symptoms intermittently for the past two years. The present attack was of one month's duration and was accompanied by severe tenesmus.

March 11, the patient had thirteen bowel movements of the characteristic dysenteric type. The following night he was given one dose of 30 drops of the benzyl benzoate. Ten stools had been passed during that day, but March 13 the patient moved his bowels four times only. The supply of benzyl benzoate on the ward had given out and, through a misunderstanding, was not renewed at that time. Ipecac treatment was started the night of March 14. That day the patient had moved his bowels five times, but there was no pain. However, he was very weak. The motions increased in frequence—possibly as a result of the laxative action of ipecac which occurs occasionally, but the increase continued together with a renewal of the tenesmus until March 17, when the patient had eleven movements. The ipecac was stopped and benzyl benzoate (of local preparation), 20 drops, three times a day, was started. There were three movements only on each of the succeeding days, pain and

tenesmus had completely disappeared, but the stools were still dysenteric and contained many endamebae and trichomonads.

The benzyl benzoate was discontinued March 21, at which time the stool was practically formed and contained only slight streaks of blood. The withdrawal of the drug was accompanied in the next four days by a growing frequency in the number of the stools, a return of the pain and tenesmus and the reappearance of blood and mucus in the stool. The night of March 25, ipecac treatment was resumed. The stools gradually decreased in number, but it was not until March 30 that the patient experienced relief from pain and the stools had become formed. The patient was permitted to go home April 2.

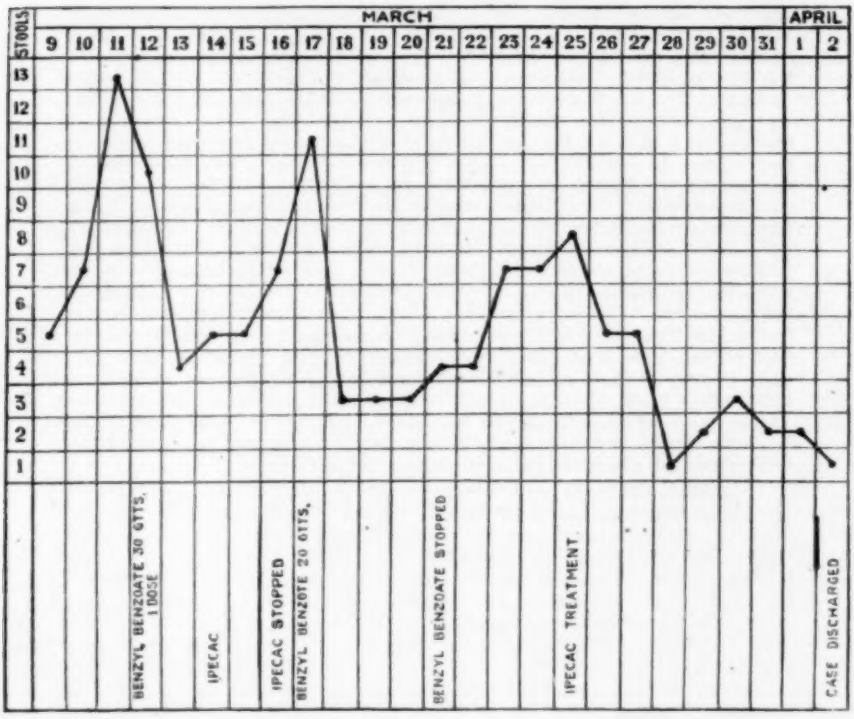
STOOLS
MARCH
APRIL
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 1 2
13 12 11 10 9 8 7 6 5 4 3 2 1
BENZYL BENZOATE 30 GTTS. 1 DOSE
IPECAC
IPECAC STOPPED
BENZYL BENZOTE 20 GTTS.
BENZYL BENZOATE STOPPED
IPECAC TREATMENT
CASE DISCHARGED

Chart of stools passed in Case 68213. Note sudden fall in number of stools following administration of one dose of benzyl benzoate March 12, and rise following administration of ipecac. Note also the sudden fall when benzyl benzoate was again given March 17, and the second rise when the drug was stopped March 21.

This case was one of the most interesting of the series for it seems to show, in a rather striking manner, the more or less positive response in the shape of the amelioration of symptoms each time benzyl is given. There is also a basis for comparison of the action of benzyl benzoate and ipecac. An attempt has been made to illustrate this graphically in the chart.

Case 67798.—Male, 19 years of age, was admitted to the hospital February 19. The cytology of the stool presented the characteristic picture of

bacillary dysentery, containing necrotic epithelium, polymorphonuclear leukocytes in abundance, blood and mucus. The only animal parasite found was *Ancylostoma duodenale*. Bacteriologically the stool was positive for *Bacillus dysenteriae* (Shiga).

This was a case of acute bacillary dysentery of the most severe type and at the outset we regarded the prognosis as exceedingly grave. The temperature at no time rose above 38.5 C., a condition we have grown to regard as rather an ominous sign in bacillary dysentery.

The onset of the attack was one week previous to admission to the hospital which did not mend matters for the patient. It started as diarrhea with black, foul-smelling stools, slight fever and chilly sensations. The stools became more and more frequent, gradually assuming a typical dysenteric character, then became more scanty in amount and, later, bloody. On admission the bowels were in almost continuous motion.

We approached the treatment of this case with benzyl benzoate with considerable hesitation. The indications for the administration of massive doses of antidysenteric serum were so apparent that treatment was started with 20 c.c. of the serum administered intramuscularly, every four hours. At the same time benzyl benzoate, 25 drops, three times a day, was given. The case ran a stormy course and it was not until February 25 that any change was noted. On that day the abdominal pain and tenesmus were markedly diminished and the patient stated that he felt much better. The following day the abdominal pain and tenesmus were still further relieved, the general condition showed distinct improvement and the stools a tendency to diminish in number. The serum was now administered only twice a day. The improvement continued and March 1 the temperature had fallen to normal, there was little pain or tenesmus and the stools were fewer in number though still numerous. The general condition of the patient was better.

From that time on the patient showed steady improvement. At times the temperature would be intermittent. March 8, the stools were becoming formed and they were fully formed three days later. The patient was then averaging one to two movements in the twenty-four hours.

We are frank to say that we can make no quantitative estimate of the effect of benzyl benzoate in this case. Judged by our experience with similar cases, we feel that the drug helped. We believe that much of the general improvement that became manifest February 25 was due to the benzyl benzoate. Though we observed no bad effects, our inclination is still to employ this drug with considerable caution in the treatment of bacillary dysentery.

DISCUSSION

We have employed benzyl benzoate in the treatment of eight cases of endamebic dysentery uncomplicated by bacillary infection and have seen markedly good results in every case. All our cases were of the acute type and varied in severity. We have not as yet tried the action of the drug in chronic cases or in the cases of "carriers" or those persons who discharge abundant cysts without showing symptoms of endamebiasis.

We have, so far, observed no ill effects on the alimentary or excretory tracts following the administration of benzyl benzoate. In no case has the drug unfavorably altered the course of any case. On the contrary, as has been said, its administration has always been accompanied by a marked alleviation of both the objective and subjective symptoms of the disease. It gives the patient much needed rest and

permits him to sleep at night, a most important desideratum in the treatment of dysentery.

Under the administration of the drug the endamebas disappeared from the stools in nearly every case as the general symptoms subsided. Whether this disappearance of the parasites is temporary or permanent remains to be demonstrated by future investigation.

There is ground for belief that benzyl benzoate possesses amebicidal properties. This has been suggested by Macht and Fisher[6] in a series of in vitro experiments. While we do not place a high value on such experiments, we consider the point is well worth working on. We can only say that this series of cases does not afford evidence which would tend to establish proof one way or the other.

We believe that in addition to relieving, to a substantial degree, some of the most distressing symptoms which accompany a dysentery attack that, in combination with ipecacuanha or its alkaloids, benzyl benzoate noticeably shortens the term of illness.

It has been shown in some of our cases that benzyl benzoate alone will bring about a complete subsidence of the symptoms of acute endamebic dysentery. Whether these cases are permanently cured or will be subject to relapse must be determined in the future. It is well known that emetin cannot be relied on to cure all cases of chronic endamebiasis and the action of benzyl benzoate adds another factor to the problem of the mechanism of the cure of endamebiasis.

There is certain evidence that when used with care, benzyl benzoate may be employed with advantage in conjunction with serum, in the treatment of bacillary dysentery. It is suggested that it may be of particular value in mixed bacillary and endamebic dysentery where the condition of the heart forbids the use of emetin.

For the present, we consider it safe to state that benzyl benzoate is, to say the very least, a valuable auxiliary to the other forms of antiamebic treatment, and that it gives real promise of usefulness when employed alone. This is entirely aside from any amebicidal powers it may, in the future, be shown to possess. It is agreeable to take, and if it can be used alone it will be a boon to the patient who suffers from the distressing nausea produced by ipecac.

We believe it is probably unwise in acute cases, especially when a bacillary involvement is present with accompanying toxemia, to push the drug to the point where the patient becomes constipated — a condition that has occurred in two of our cases of uncomplicated endamebiasis.

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6. Macht, David I., and Fisher, E.: J. Pharmacol. & Exper. Therap. **11**: 263 (April) 1918.

Benzyl benzoate seems to take the place of morphin in dysentery in that it slows the peristalsis and relieves the pain and tenesmus; but it shows none of the undesirable traits of opium. It is slower in its effects than opium and, of course, obviates the danger of habit formation in a susceptible patient. The sedative action of the drug on the intestinal musculature seems to us to be of preeminent importance. The violent peristalsis is promptly quieted and the intestine is given rest and a chance to carry out the normal reparative processes. It is possible that the spread of the infection is also distinctly limited through the quieting of the gut. Rest for the intestine seems to us to be fully as important as bodily rest for the patient secured by keeping him in bed.

So far as we have observed, benzyl benzoate exerts no effects on any of the intestinal protozoa other than *Endameba dysenterica*, neither were the intestinal helminths encountered affected by it.

CONCLUSIONS

It seems evident that benzyl benzoate exerts a definite and favorable influence on the course of endamebic dysentery. The question arises as to how this effect is brought about. Among the points that should be determined in the future are the following:

1. Its action on chronic and "carrier" cases and in hepatic endamebiasis as well as endamebic involvement of the urinary system and other organs.

2. The determination of the minimum effective dose, and the action of larger doses than we have given.

3. Its effects on the hemopoietic system.

4. Has the drug specific amebicidal properties, possibly through the splitting off of one or more of its radicals in metabolism? If such is the case a curative action may be expected.

5. Is the effect more on the host than on the parasite? That is to say, does it have a tendency to restore the normal equilibrium between parasite and host with accompanying subsidence of the acute symptoms and assumption of a state of chronicity, but without sterilization of the patient? Under such circumstances relapse to an acute condition may be expected sooner or later.

6. Does the sedative action of the drug on the intestinal musculature merely limit the spread of the infection and possibly permit some undetermined body defense to regulate the infection?

7. Is there a possibility of synergistic action between benzyl benzoate and ipecacuanha and its alkaloids, or, is it possible that benzyl benzoate tends to make the endameba more sensitive to the action

of ipecac and emetin? In this connection attention is drawn to Case 68313.

In conclusion, we desire to extend our thanks to Dr. Ariston Bautista y Lim, head of the department of medicine on whose service these patients were assigned, for permission to study them, and to Drs. Facundo Esquivel, F. R. Fernandez de Leon and Wenceslao Vitug of the house staff for substantial assistance rendered.

ADDENDUM

TWO CASES OF ENDAMEBIC DYSENTERY AT BAGUIO HOSPITAL TREATED WITH BENZYL BENZOATE

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BAGUIO

These two cases of acute endamebic dysentery were treated by me at the Baguio Hospital at the instance of Professor Haughwout, who furnished me with a supply of benzyl benzoate miscible in 20 per cent. alcoholic solution. They are of some interest inasmuch as one of the patients received emetin compounds in addition to the benzyl benzoate, while the other was treated with the benzyl benzoate alone.

The following is a report of my cases:

REPORT OF CASES

CASE 1.—C. Y., a Spanish mestiza, 31 years of age, had dysentery six or seven months ago at which time her stool was reported positive for *Endamoeba dysenterica*. Two physicians treated her at that time by both hypodermic and intravenous administration of emetin hydrochlorid. She suffered three relapses. The patient came to Baguio and two days later came down with another acute attack. Her stool contained an abundance of mucus and blood and a large number of actively motile endamebas.

I gave her six injections of emetin, in one-half grain doses, and, she having failed to improve, gave her in all, six grains of emetin bismuthous iodid. Examination of the stool following this treatment, showed numerous cysts of *Endamoeba dysenterica*, but three days later she came down with another acute attack. I continued the treatment with emetin bismuthous iodid, giving her 12 grains in all. About a week after the discontinuance of the drug, she had another acute attack, and, as in the previous instance, had from ten to fourteen bowel movements a day. These were accompanied by intense griping pains in the abdomen, intense burning pain in the region of the rectum, accompanied by distressing tenesmus.

At this period I started her on the benzyl benzoate, 10 drops three times a day. After taking three doses of the benzyl benzoate the number of bowel movements fell to four. The stools still contained mucus, slightly streaked with blood and endamebas. The abdominal pain and distress were by this time markedly diminished. The second day the patient had but one movement of a semisolid nature. Pain in the abdomen had disappeared almost altogether as had the pain in the rectum.

However, the stools still bore traces of mucus and contained few endamebas, so I put her on emetin again, giving her, in all, 2 grains of the hydrochlorid and 6 grains of the emetin bismuthous iodid.

At the end of a week two stool examinations failed to show the presence of blood, mucus or endamebas. Two examinations by the concentration method of Cropper and Row failed to show the presence of cysts.

CASE 2.—J. S., Filipina, 24 years of age, was already under treatment in the hospital for pulmonary tuberculosis. She was in the second stage of that disease. She developed endamebic dysentery, her stool showing an abundance of mucus, blood and active *Endamoeba dysenterica*. She was passing eight to ten stools a day. These were accompanied by distressing gripping pains in the abdomen, burning pain in the rectum and tenesmus. On the second day of the illness I started her on 10 drops of the benzyl benzoate, three times a day. Following the first three doses the daily number of stools fell to two. These were of semi-solid character, but still contained mucus, blood and endamebas. The parasites were very sluggish in their movements. No cysts were found. The pain was much diminished in intensity, but had not disappeared. On the second, third and succeeding days the bowel movements were normal and no endamebas were found either as trophozoites or encysted forms. All pain and distress had disappeared.

COMMENT

The first case was the more severe of the two. Treatment included the administration of emetin bismuthous iodid, and later emetin hydrochlorid, but under it little, if any, improvement was noted in the symptoms. Later, emetin hydrochlorid was combined with benzyl benzoate which brought about a complete and speedy subsidence of all the symptoms and the disappearance of the parasites from the stool.

No emetin was given to the second patient. Under treatment with benzyl benzoate the symptoms rapidly disappeared and, with them, the endamebas in both the trophozoite and encysted forms disappeared.

A STATISTICAL DISCUSSION OF THE RELATIVE EFFICACY OF DIFFERENT METHODS OF TREATING PNEUMONIA*

RAYMOND PEARL
BALTIMORE

Recently Head[1] contributed an interesting discussion of the results of treating post-influenzal pneumonia by the open as contrasted with the close ward method. The general result apparently was to show that the latter method was greatly superior to the former, as evidenced by the case fatality rates under the two modes of procedure. While the author definitely draws this conclusion and states with confidence that the study of the 1,400 cases he dealt with "points the way to the more successful management of this disease," he also raises a rather obvious point of criticism to the results as they stand, using the following words:

> The question at once arises, Is the lowered mortality here shown in favor of the closed ward treatment a real gain in the management of the disease over the open ward method, or are the favorable results only a coincidence, an expression of a lowered mortality arising naturally in the latter part of the epidemic? It has been stated by Abrahams, Hallows and French that the mortality is higher and the disease more severe in the early part of epidemics of influenza complicated by pneumonia.

The problem raised is an interesting one statistically, and one of a sort which continually arises in medical literature. A new method of treatment for a disease is devised and tried in a number of cases with a case fatality rate lower, by a greater or smaller amount, than the case fatality rate which had prevailed under some other mode of treatment. The problem in any such case is this: Is the lowering of the case fatality rate in the new circumstances so great that it cannot reasonably be supposed to have arisen by chance alone? Usually, no adequate evidence on this point is given by the physician, chiefly for the reason that he has no technical knowledge of the proper mathematical tests to apply. The potency of random sampling in bringing about divergences is apparently but little understood outside of professional statistical circles.

As an illustration of the effects of random sampling let us consider a hypothetical case. In any large city, or a state, or indeed, any large population aggregate, the average age at death of persons dying at the same calendar date should be identical for all dates, except for the influence of two factors, viz: (a) chance, or random sampling, and (b) long seasonal waves arising from the fact particularly that rela-

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* Papers from the Department of Biometry and Vital Statistics, School of Hygiene and Public Health, Johns Hopkins University, No. 6.

1. Head, G. D.: Treatment of Pneumonia, J. A. M. A. **72**:1268 (May 3) 1919.

tively more infants die in hot summer weather than in the colder seasons of the year. In any short period, say ten consecutive days, the second factor (b) would not operate, and we should expect the persons dying on each of these consecutive ten days to show the same average age, except for the fluctuations due to chance alone. How considerable these fluctuations may be is shown in Table 1, which gives the number of deaths and the average age at death of those dying during ten consecutive days in 1916 in Baltimore.[2]

TABLE 1.—MEAN AGE AT DEATH OF THOSE DYING IN THE STATED DAYS IN BALTIMORE

Date	Number of Deaths	Mean Age at Death in Years
Jan. 13, 1916	31	30.16
14	40	43.80
15	27	40.59
16	48	48.21
17	32	48.34
18	41	51.90
19	29	46.82
20	31	52.39
21	39	51.62
22	57	39.40
Total for the year	10,668	39.83

Here we have a fluctuation in the average, based on samples of from thirty to fifty individuals, amounting to more than twenty-two years, arising from random sampling alone. Such an illustration emphasizes the fact that before conclusions can safely be drawn from differences between numbers it is necessary to know something about the "probable errors" of those numbers.

The particular theorem in probability which is applicable in problems of the type exemplified in Head's paper referred to above was first set forth by Pearson.[3] I have recently discussed this subject further.[4]

Let it be supposed that a first sample of $n = p + q$ be drawn from the population, p denoting the number of times the event dealt with occurs in the n trials, and q the number of times it fails.

Write

$$\bar{p} = \frac{p}{n}, \quad \bar{q} = \frac{q}{n},$$

whence of course

$$\bar{p} + \bar{q} = 1.$$

We then have for the chief constants of the error distribution for a second sample, of magnitude m, drawn from the same population the following values:

2. I am deeply indebted to Dr. John H. Blake, Commissioner of Health, and Dr. W. T. Howard, Assistant Commissioner of Health of Baltimore, for kindly allowing me the use of the records of the Health Department for the study of this and other problems now being investigated in this laboratory.

3. Pearson, K.: Phil. Mag., March, 1907, p. 365.

4. Pearl, R.: Amer. Nat. **51**:144, 1917.

$$\text{Mean}^5 = m\bar{p} + \frac{m}{n+2}(\bar{q} - \bar{p}), \tag{i}$$

$$\text{Mode} = \text{the integral portion of } m\bar{p} + \bar{p} \tag{ii}$$

$$\text{Standard deviation} = \left\{ m \left[\bar{p} + \frac{\bar{q} - \bar{p}}{n+2} \right] \left[\bar{q} - \frac{\bar{q} - \bar{p}}{n+2} \right] \left[1 + \frac{m-1}{n+3} \right] \right\}^{1/2} \tag{iii}$$

These values are entirely general and independent of the values of n, m, p and q. Under certain circumstances, as when n is very large as compared with m, and neither p nor q is very small, (i) and (iii) are obviously capable of being put in much simpler form and still giving a sufficiently close approximation to the true result.

Let us now apply this theorem to the data given by Head.[1] From the figures he gives we may state the problem in these terms: If under the open ward treatment, out of a sample of 966 patients with acute pneumonia 135 died, what would be the probable number to die in a second sample of 435 acute pneumonia patients from the same population, given the same treatment?

We have here, in our mathematical notation

$$\begin{aligned} n &= 966 \\ m &= 435 \\ p &= 135 \\ q &= 831 \\ \bar{p} &= \frac{135}{966} = .1397 \quad \bar{q} = \frac{831}{966} = .8603 \end{aligned}$$

Whence from (i) and (ii) we readily deduce

Mean deaths expected in second sample $= 61.12 \pm .28$
Modal, or most probable number of deaths in second sample $= 61$
Standard deviation $= 8.72$

But the actually observed number of deaths in the second sample, under the close ward treatment, was fourteen instead of sixty-one. Hence we may safely conclude that under the close ward treatment significantly fewer persons died than would have been expected to die on the basis of chance, if the same force of mortality had prevailed in the latter period as did in the former.

But can it be assumed that the same force of mortality was impinging, and its results were mitigated only by the new method of treatment? As we have seen, Head himself expresses some doubt on this point, and surely no safe conclusion as to the merits of the treatment can be drawn until this point is settled. In order to settle it we have used data from a comparable outbreak of post-influenzal pneumonia where the same treatment was followed throughout the outbreak. Would there be in such a case a falling off of the case-fatality rate in the latter part of the epidemic corresponding entirely or in some degree to that observed by Head? Through the kindness of

5. From the origin at the lower range end, or $r = 0$.

Dr. Eugene L. Opie, to whom I wish to express my indebtedness, I am able to present data of this sort for the Camp Pike epidemic.

Table 2 gives the cases and deaths in the Camp Pike epidemic. The cases have already been published by Opie[7] *et al.* The deaths by days he kindly furnished me in manuscript.

TABLE 2.—CASES AND DEATHS OF PNEUMONIA AT CAMP PIKE, ARK., FROM SEPT. 1 TO OCT. 31, 1918

Day September	Cases of Pneumonia	Deaths from Pneumonia	Day October	Cases of Pneumonia	Deaths from Pneumonia
1	1	0	1	126	16
2	3	0	2	142	11
3	2	0	3	113	20
4	1	0	4	129	32
5	3	0	5	86	20
6	3	1	6	89	22
7	4	0	7	93	29
8	3	0	8	76	30
9	1	0	9	42	30
10	3	0	10	66	28
11	4	0	11	54	32
12	1	0	12	34	20
13	4	0	13	15	18
14	7	1	14	13	13
15	10	0	15	9	13
16	10	0	16	19	11
17	7	0	17	8	8
18	5	3	18	8	8
19	11	..	19	9	7
20	12	..	20	11	1
21	10	1	21	5	5
22	13	1	22	6	1
23	15	5	23	11	5
24	13	3	24	5	8
25	25	3	25	7	2
26	16	0	26	3	0
27	23	0	27	1	5
28	20	3	28	1	1
29	40	11	29	3	1
30	35	11	30	0	1
			31	0	0
Totals.....				1,499	441

In order to treat these data in a way comparable to the others, it is necessary to divide the epidemic at a corresponding point. In the Camp Wheeler epidemic (Head's data) the change in treatment occurred after 966 out of 1,401 cases had occurred. The same stage of the Camp Pike epidemic was reached $\frac{966}{1,401} \times 1,499 = 1,034$ cases had occurred. The nearest date to this point, as can be determined by summing the "case" columns of Table 2, is October 6. At the end of that day 1,000 cases of pneumonia had occurred in the Camp Pike epidemic. We may then take through October 6 as the first phase of the Camp Pike epidemic, so far as concerns cases, this phase corresponding to the "open ward" period of the Camp Wheeler data. We have next to consider the deaths which belong to these 1,000 cases occurring prior to the end of October 6. In general, it appears from the data in hand that there was, on the average, a lag of about eight

7. Opie, E. L., Freeman, A. W., Blake, F. G., Small, J. C., and Rivers, T. M.: J. A. M. A. **72**:556 (Feb. 22) 1919.

days between case and death curves in the epidemic of post-influenzal pneumonia in camps. Accepting this figure, as in accord to a first degree of approximation at least, with the facts, we have October 14 as the date for dividing the Camp Pike death curve into two portions, which will correspond approximately to the two different treatment moieties of the Camp Wheeler data.

In the same notation as before we have for Camp Pike:

Cases of pneumonia through October 6 $= n = 1{,}000$
Deaths from pneumonia through October 14 $= p = 364$, whence $q = .636$, and $\bar{p} = .364$, and $\bar{q} = .636$
Cases of pneumonia beginning October 7 and going to end of the epidemic $= m = 499$

The problem then may be stated in this way: If, with no change of treatment, 364 patients died out of a sample of 1,000, what is the probable number of deaths in a second sample of 499 cases? By the same method as before the data give

Mean deaths expected in second sample $= 18.77 \pm .40$
Modal, or most probable number of deaths in second sample $= 182$
Standard deviation $= 13.15$

Now, the actual number of deaths in the last 499 cases of the Camp Pike epidemic was only seventy-seven instead of the expected 182. But there had been no change in method of treatment. Hence, it is clear that the statement of Abrahams, Hallows and French, quoted from Head at the beginning of this paper, is true. Fewer deaths in proportion to cases occur in the later as compared with the earlier portion of these epidemic outbreaks, quite without change of treatment.

This result obviously tends to cast reasonable doubt on the efficacy of the close ward as compared with the open ward treatment of these epidemic pneumonias. It is necessary, however, to make a further quantitative comparison before drawing any final conclusion. In the second sample (latter part) from the Camp Pike epidemic the actual deaths formed 42 per cent. of the deaths expected on the basis of chance from the results shown in the first sample from the same epidemic ($\frac{77 \times 100}{182} = 42$ per cent.). In the Camp Wheeler epidemic (Head's data) the actual deaths under the close ward treatment formed only 23 per cent. of the deaths expected on the basis of chance from the results shown in the first sample from the same epidemic, under the open ward treatment ($\frac{14 \times 100}{61} = 23$ per cent.).

This result gives the significant comparison. The whole matter may be summarized in this way. While it is true that the case fatality rate tends under a constant form of treatment to be markedly lower in the later portions of epidemic outbreaks of pneumonia, nevertheless Head's data show, when given proper mathematical analysis, that under the close ward treatment only about half (23 per cent. versus

42 per cent.) as many deaths occurred relatively in the latter part of the epidemic as would have occurred under the open ward method of treatment, after making allowance for the normally diminishing case fatality rate of later portions of the epidemic. To that degree, then, Head's conclusions are justified, and obviously constitute an important contribution to the sum of medical knowledge regarding the proper treatment of pneumonia.

COMMENT

The first purpose of this paper is to find out, by appropriate mathematical treatment of the data, the real truth as to the relative merits of two methods of treating epidemic pneumonia. Because of the lack of such analysis the results as originally published by Head, comparing the open ward and close ward treatments, were scientifically inconclusive.

The second purpose of the paper is to illustrate by a concrete example, not only the importance, but indeed the absolute necessity of mathematical tests of the validity of results and conclusions, if medicine is ever to measure up to the standards of scientific logic and accuracy which prevail in some, at least, of the other branches of biologic and physical science. Many, indeed most, of the problems of practical medicine in a broad sense are either essentially statistical problems, or their statistical phase is a vitally important one in reaching correct conclusions. The medical man is thoroughly familiar with the necessity for clinical and laboratory tests. Only in rare instances does he realize the necessity of applying to his results before drawing conclusions from them, whether for purposes of publication or practice, a proper test for the magnitude of the probable errors arising from random sampling. It is a commonplace of medical literature to find the most positive and sweeping conclusions drawn from a sample so meager as to make scientifically sound conclusions of any sort utterly impossible. It is not too much to say that the investigator in the field of medicine should be as familiar with the probable error test as he is with the Wassermann test.

SUMMARY

In this paper it is shown that in deciding as to the merits of different methods of treatment of a disease it is necessary to take account of the probable errors arising from random sampling. In the case of Head's results on the pneumonia epidemic in Camp Wheeler the reduction in the fatality rate following the institution of the close ward treatment is shown to be only in part a result of the treatment, the remainder being the normal reduction in the case-fatality rate in the later portion of epidemics.

THE BASAL METABOLISM IN HYPOTHYROIDISM *

J. H. MEANS, M.D., AND J. C. AUB, M.D.

BOSTON

In connection with an extended study of the basal metabolism in exophthalmic goiter, which has been in progress since 1914 and on which a preliminary report was published in the spring of 1917,[1] opportunities arose to study several cases of hypothyroidism.

The present series comprises observations on six patients and includes practically every condition clinically associated with hypothyroidism, namely, myxedema, cretinism, cachexia strumipriva, and cancer of the thyroid gland. The effect of thyroid administration on the basal metabolism has been studied over a long period of time in the case of a cretin and in one patient with myxedema; also in a patient with cachexia strumipriva, before, during and after the appearance of hypothyroid symptoms.

The methods employed have been fully described in earlier papers,[2] and consisted briefly in the determination of the gas exchange of the recumbent subject while in the postabsorptive condition by means of the small Benedict apparatus and the calculation of the heart production therefrom.

The metabolism data are all shown in the table, the figures for any one day being the average of at least two and usually of three ten minute periods on the Benedict apparatus. The heat production is calculated from the oxygen absorption and the respiratory quotient obtained, except in a few instances where oxygen alone was determined, in which case a respiratory quotient of 0.82 has been assumed.

The body surface figures are obtained from DuBois' height-weight chart,[3] and the figures for standard basal metabolism are those adopted by the workers at the Russell Sage Institute of Pathology.[4]

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* From the Medical Service of the Massachusetts General Hospital, aided in part by a grant from the Proctor Fund, Harvard Medical School.

1. Means, J. H. and Aub, J. C.: Study of Exophthalmic Goiter from the point of view of the Basal Metabolism, J. A. M. A., **69**: 33 (July 7), 1917.

2. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, J. Med. Res. **32**:121, 1915. Means J. H.: Studies of the Basal Metabolism in Disease and their Importance in Clinical Medicine. Boston M. & S. J. **174**:864 (June 15), 1916.

3. DuBois, D., and DuBois, E. F.: Clinical Calorimetry, X, Arch. Int. Med. **17**: Part ii, 863 (June), 1916.

4. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry, XIX, Arch. Int. Med. **19**: 823 (May), 1917.

CASE REPORTS[5]

CASE 1.—*Myxedema.* (Lab. No. 2, Hospital No. 198463, W. M.) Mrs. D., a housewife, 57 years of age, first came under our observation October 1, 1914. Six years previously she had been in the hospital with a history of dyspnea and edema of the face and legs, present for four years. A diagnosis of anasarca and ascites was made at that time, but, nevertheless, myxedema was suspected and she was told to take thyroid extract but did not do so.

September 30, 1914, she again entered the hospital. The same symptoms had persisted during the interval and had increased in severity. She was getting dull mentally, so her relatives said, and complained frequently of feeling chilly. Physical examination showed the typical picture of myxedema. The subcutaneous tissue was thickened throughout; there was marked puffiness about the eyes, and fat pads about the neck and shoulders. The skin was dry and scaly, the hair sparse and quite coarse and brittle. The physical examination in other respects was not remarkable. The blood pressure, the blood picture and cell counts, and the urine examination were all quite normal. The Wassermann (blood) was negative and roentgenogram of the head showed a normal sella turcica.

October 2, 1914.—Basal metabolism 28 per cent. below normal.

October 5, 1914.—Second metabolism determination 33 per cent. below normal. Following this thyroid administration was begun. Thyroid extract, 4½ grains, was given on this date.

October 7 and 8, 1914.—Thyroid extract, grains 6, daily.

October 9, 1914.—Thyroid extract was increased to grains 7½ daily.

October 11, 1914.—Basal metabolism, 9 per cent. below normal.

October 18, 1914.—Discharged on thyroid extract, grains 7½, daily.

November 2, 1914.—Readmitted to hospital. Since discharge she had taken thyroid extract, grains 7½, daily. She had been troubled with anorexia, nausea and vomiting. She was emaciated and her breath had a slight odor of acetone. The myxedematous appearance was gone.

November 3, 1914.—The electrocardiogram showed a normal rhythm, and an upright "T" wave in Lead II. There was indication also of left ventricular preponderance.

November 4, 1914.—Basal metabolism was 3 per cent. above normal. Thyroid extract was discontinued.

November 7, 1914.—Vomiting had ceased, and she appeared to be well. Discharged on thyroid extract, grains 1½, per day.

October 31, 1916.—The patient called at the hospital in response to a letter. She had been taking thyroid extract, grains 1½, every day since November 7, 1914, except for one or two short periods when her supply of tablets was exhausted. She has felt very well and was alert mentally. Her appetite was good. She perspired like a normal individual. She was not chilly. Her hair fell out and her skin desquamated two years ago, but now she has normal skin and a good growth of new hair. She was ordered to take thyroid extract, 1½ grains per day half the time and 3 grains per day the remainder of the time.

January 15, 1917.—She came to the hospital for a metabolism determination. This showed a result 11 per cent. above the normal. Since her last visit she had been taking thyroid extract, grains 3, per day about three fourths of the time, and 1½ grains per day about one fourth the time. She felt and looked well. There were no symptoms of either hypothyroidism or hyperthyroidism. Since her metabolism was higher than it ever had been before she was directed to reduce the dose of thyroid extract to 1½ grains per day.

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5. One observation on Mrs. D. was published by Means, J. H.: Proc. Soc. Exp. Biol. & Med. **12**: 13, 1914, and four by Means, J. H.: Boston M. & S. J. **174**: 864 (June 15), 1916, where she was designated Case 10. Also the three observations on Mrs. R. were given in the last mentioned paper, Case 11, but in an incomplete form.

Metabolism Data Obtained in Cases of Myxedema, Cretinism and Cachexia Strumipriva

Date	Age	Height, Cm.	Weight, Kg.	Body Surface (Du Bois Height-Weight Chart) S. M.	Oxygen, C.c. per Min.	Carbon Dioxid, C.c. per Min.	Respiratory Quotient	Pulse	Total Calories per Hour	Calories per Square Meter per Hour	Normal Standard Calories per Sq. M. per Hour	Variation, per Cent.	Remarks
Mrs. D. (Case 1) Myxedema													
10/ 2/14	57	153.0	67.0	1.65	144	115	0.80	58	41.5	25.1	35.0	—28	Treatment not begun. Typical myxedema
10/ 5/14	57	153.0	67.0	1.65	130	119	0.91	63	38.5	23.3	35.0	—33	No thyroid yet
10/11/14	57	153.0	64.5	1.62	182	131	0.72	69	51.4	31.7	35.0	— 9	Total of 36 grains of thyroid extract since last observation
11/ 4/14	57	153.0	59.0	1.56	199	148	0.74	65	56.4	36.1	35.0	+ 3	On thyroid extract, 7½ grains daily since last observation. Myxedematous appearance gone
1/15/17	59	152.5	68.5	1.66	225	180	0.80	80	64.8	39.0	35.0	+11	Until Oct. 31, 1916, took thyroid extract, 1½ grains daily. Since then 3 grains daily three fourths of the time, and 1½ grains daily the rest
3/25/19	61	151.0	72.5	1.68	169	Not determined	0.82 Assumed	54	48.9	29.1	34.0	—14	Since last observation has been taking thyroid extract, 1½ grains per day, steadily. Skin dry but mentally alert
Miss L. (Case 2) Cretin													
2/14/17	20	137.2	39.5	1.21	126	103	0.82	95	36.5	30.1	37.0	—19	Treatment not begun. Typical cretinism
2/23/17	20	137.3	39.5	1.21	118	103	0.87	80	34.6	28.6	37.0	—23	No thyroid yet
2/27/17	20	137.2	40.2	1.20	146	121	0.83	87	42.3	35.3	37.0	— 5	Total of 12 grains of thyroid extract since last observation
3/ 2/17	20	137.2	39.6	1.21	155	128	0.83	98	45.0	37.2	37.0	+ 1	Total of 13.5 grains of thyroid extract since last observation
3/ 7/17	20	137.2	37.9	1.19	164	125	0.76	92	46.8	39.3	37.0	+ 6	On thyroid extract, 4½ grains daily since last observation
3/16/17	20	137.5	38.6	1.20	159	119	0.75	87	45.2	37.7	37.0	+ 2	On thyroid extract, 1½ grains daily since last observation. Brighter
4/24/17	20	138.0	35.9	1.17	178	147	0.83	81	51.6	44.1	37.0	+19	On thyroid extract, 1½ grains daily since last observation. Skin no longer dry
10/ 4/17	20	138.0	39.5	1.22	173	135	0.78	88	49.6	40.7	37.0	+10	On thyroid extract, 1½ grains daily since last observation
3/24/19	22	139.5	42.0	1.26	144	Not determined	0.82 Assumed	67	41.6	33.0	37.0	—11	Took thyroid extract, 1½ grains daily, until June, 1918. None since

Miss N. (Case 3) Cachexia strumipriva													
2/17/16	36	167.0	52.0	1.57	175	116	0.66	72	49.2	31.3	36.5	—14	Hemithyroidectomy Dec. 28, 1915. Second operation Feb. 1, 1916. No appearance of myxedema yet
5/ 5/16	36	167.0	60.0	1.67	177	153	0.86	71	51.8	31.0	36.5	—15	Became myxedematous since last observation. Taken 24 grains of thyroid extract in last eight days
5/29/16	36	167.0	61.3	1.69	224	164	0.73	70	63.4	37.5	36.5	+ 3	On thyroid extract, 3 grains daily, since last observation. Myxedematous appearance gone
Mrs. R. (Case 4) Myxedema													
11/13/14	41	160.5	60.0	1.63	180	137	0.76	75	51.3	31.4	36.0	—13	Treatment not begun. Typical myxedema
11/14/14	41	160.5	60.0	1.63	151	125	0.83	69	43.8	26.9	36.0	—25	No thyroid yet
11/23/14	41	160.5	Lost	1.63	171	139	0.81	82	49.4	30.5	36.0	—16	Total of 21 grains of thyroid extract since last observation. Myxedematous appearance less marked
Mrs. G. (Case 5) Myxedema													
6/28/16	63	162.7	67.0	1.72	167	133	0.80	72	48.1	28.0	34.0	—18	Treatment not begun. Mild grade of myxedema
Mr. B. (Case 6) Carcinoma of thyroid													
10/31/16	56	175.3	69.0	1.84	189	166	0.88	72	55.6	30.2	37.5	—19	Before operation
12/21/16	56	175.3	65.0	1.80	193	Not obtained	0.82 assumed	68	55.9	31.6	37.5	—17	Partial thyroidectomy Nov. 4, 1916

March 25, 1919.—She again called at the hospital in response to a letter. She had been taking thyroid extract, 1½ grains per day, ever since her last visit two years ago. Her general health had been good in the interim. She was gaining in weight. Her skin was somewhat dry but her expression was alert and she was bright mentally. Her basal metabolism was found to be 14 per cent. below the normal, so she was directed to increase the dose of thyroid extract to grains 3 every day for a week and on alternate weeks 1½ grains per day.

April 22, 1919.—She called to have her photograph taken (Fig. 1). She has been carrying out directions and feels entirely well.

Fig. 1.—Case 1. A. was taken in October, 1914, before treatment was begun. B. was taken in April, 1919, after four and one-half years of treatment.

Case 2.—*Cretinism.* (Lab. No. 142. Hospital No. 213318, E. M.) Miss L., a dwarf, 20 years of age, first entered the hospital February 13, 1917. Her family history was unimportant.

Personal history.—She had always been well but never was very strong. When 8 years of age she began to grow obese. When 10 years of age she had reached her present height. She has always felt the cold and been fond of many covers at night. She has always perspired very little. She gave a history of having had a complete set of milk teeth, followed by four upper and eight lower permanent teeth; the remainder of her present teeth are of the first set.

She went to school first when 5 years of age, and graduated from high school at 20. She had menstruated normally since 13 years of age.

Examination.—Physical examination showed a short, solidly built woman, whose short stature was not due to a relative shortening of either trunk or legs. Her arms reached midway between the hip and the knee. She was mentally bright but not vivacious. Her hands and feet were of normal shape and small in proportion to her height. Her head was square with wide face and broad cheek bones. The bridge of the nose was depressed and the forehead broad. The eyes had a slightly mongolian outline. The teeth were in fair condition, the posterior ones being small and poorly developed, the anterior ones being fairly widely spaced. The neck was short with marked double chin; the thyroid was not palpable. At the sides of the neck and over the more

prominent vertebrae there were marked pads of fat. The hair was dry and brittle, but not coarse. There was no axillary hair; the pubic hair was scanty and her eyebrows were sparse. Her skin was dry and somewhat harsh, particularly over the extremities. The breasts were fairly developed, about like those of a girl at puberty. The abdomen was fat and protuberant, especially below the umbilicus. In other respects the physical examination was negative.

The blood and urine examinations were not remarkable and the Wassermann (blood) was negative. Roentgenograms of the skull showed a normal sella turcica, those of the wrists and hands showed the lower epiphysis of the radius and ulna, and all those of the metacarpals and phalanges ununited.

February 14, 1917.—Basal metabolism was 19 per cent. below normal. The electrocardiogram showed normal rhythm and an inverted "T" wave.

February 23, 1917.—Basal metabolism was 23 per cent. below normal. Following the determination, thyroid extract, grains 3 per day, was started.

February 27, 1917.—Basal metabolism was only 5 per cent below normal. Thyroid extract was increased to grains 4½ per day.

March 2, 1917.—Basal metabolism was 1 per cent. above normal.

March 7, 1917.—She has been on thyroid extract, grains 4½, since the last observation. Basal metabolism was 6 per cent. above normal. No symptoms of hyperthyroidism were present but she has lost a little weight. The electrocardiogram showed a normal rhythm and the "T" wave was no longer inverted. It was merely flat. Thyroid extract was reduced to 1½ grains per day.

March 14, 1917.—The electrocardiogram showed a normal rhythm and a "T" wave 2 mm. high.

March 16, 1917.—Basal metabolism was 2 per cent. above normal. She was much brighter. Discharged on thyroid extract, 1½ grains per day.

April 24, 1917.—She called at the hospital for observation. Basal metabolism was 19 per cent. above normal. The electrocardiogram was as on March 14. Her eyes were brighter and the pads of fat on her back were gone. Her hands were moist and warm.

October 4, 1917.—Patient called again at the hospital for observation. She had been taking thyroid extract, 1½ grains per day, since last observation. The basal metabolism was 10 per cent. above normal.

March 24, 1919.—Patient came to the hospital in response to a letter. She continued to take thyroid extract, 1½ grains per day, until June, 1918. Then her supply of tablets was exhausted and she had taken none since. She felt quite well, was living at home and doing housework. She was bright, and alert mentally. Her appearance was, however, not very different from what it was when she first came under observation; her hair was dry and brittle, but not falling out; the skin was dry but there was some moisture in the palms of the hands. She had menstruated normally since her last visit. She had increased in height by 2.3 cm. since the time when thyroid therapy was first started. Her basal metabolism was 11 per cent. below normal, therefore she was told to take thyroid extract again, 1½ grains daily.

CASE 3.—*Cachexia Strumipriva.*—(Lab. No. 54. Hospital No. 208010, W. S.) Miss N., a graduate nurse, 36 years of age, first came under our observation February 16, 1916. She had previously been a patient in the hospital and had had two operations on the thyroid gland. She was first admitted to the ward December 7, 1915.

Previous history.—From the time she began to menstruate at 14 years of age she had noted some slight fullness in the region of the thyroid. This remained stationary and was not accompanied by other symptoms until a week before her entry into the hospital, at which time she found that her neck was increasing in size and was tender to touch. For three days she had been very depressed and nervous.

Examination.—Physical examination showed the thyroid considerably enlarged, somewhat more on the left side than on the right. It was slightly tender. Over the right lobe a musical hum was heard, which was accentuated during systole. In other respects the physical examination was negative and none of the usual signs or symptoms of hyperthyroidism were present. The Wassermann test was negative. The urine showed a moderate amount of albumen and a few casts.

She remained in the medical wards for a time, with an irregular, septic type of temperature curve, and a white count varying between ten and fourteen thousand. It was finally decided to resort to surgery.

Operation.—December 28, 1915.—Operation under gas and oxygen by Dr. G. W. W. Brewster. The right lobe of the thyroid was exposed and resected, a small bit of normal gland being left at the superior border. The lobe was found to be enlarged and hard and did not bleed when incised. The patient stood the operation well.

Pathologic Report.—The removed tissue was examined. It consisted of a portion of two lobes, the largest 7x2.5 cm., the smaller 2x4 cm. The surface was smooth, firm, and hard. Section was white with small, reddish brown areas. Microscopic examination showed a round cell infiltration about the follicles, with atrophy. In some places the remnants seem as masses of rather large, degenerated cells; in other places with remnants of colloid and occasional giant cells. The anatomic diagnosis was thyroiditis.

She continued to run a septic temperature and was not by any means cured.

Second operation.—February 1, 1916, a second operation was performed under gas and oxygen anesthesia by Dr. G. W. W. Brewster. The left lobe of the thyroid was exposed. It was found to be enlarged and smooth, very firm and whitish in color. About six sevenths of this lobe was resected. Small bits of normal looking thyroid tissue were left at the isthmus and attached to the posterior wall of the capsule. The patient made a good recovery from the operation.

Pathologic Report.—This lobe measured 8x4.5x4 cm. One surface was irregular. On section the tissue was firm, yellowish gray in color, with small areas of yellowish softening. Microscopic examination showed the tissue between the follicles to be thickened, infiltrated with round cells and in places containing large multinucleated bodies. The follicles in many places were atrophied and in others they contained a little detritus. The anatomic diagnosis was chronic thyroiditis.

February 17, 1916.—The patient made an uneventful operative recovery. On this date the basal metabolism was 14 per cent. below normal, but she had not yet developed any clinical manifestations of hypothyroidism.

March 6, 1916.—Patient was discharged from the hospital apparently in good health.

April 24, 1916.—She was again admitted to the hospital with the story that three weeks previously she had begun to get some puffiness of the face and hands. She also began to feel lazy and dull and her skin became dry.

Physical examination showed the typical picture of myxedema. She was mentally sluggish, her skin was dry and harsh. Her tongue was thickened and her face and hands were puffy. Her hair was not altered particularly. There had been no iregularities in her catamenia. She had gained twenty-five pounds in weight since her second operation.

April 27, 1916.—She started on thyroid extract, 1½ grains per day.

April 30, 1916.—Thyroid extract was increased to 3 grains per day.

May 2, 1916.—Thyroid extract was increased to 4½ grains per day.

May 5, 1916.—Basal metabolism was 15 per cent. below normal.

May 9, 1916.—Patient was much brighter; myxedematous appearance was less marked. Discharged on thyroid extract, 3 grains per day.

May 29, 1916.—She called at the hospital for observation. She had been taking thyroid extract, 3 grains per day, since her discharge. Her condition was very much better. The myxedematous appearance was quite gone. The skin was moist and she was bright and alert mentally. The only evidence of hypothyroidism was that her hair was somewhat coarse, more so in fact than when she was last seen. The basal metabolism was 3 per cent. above normal.

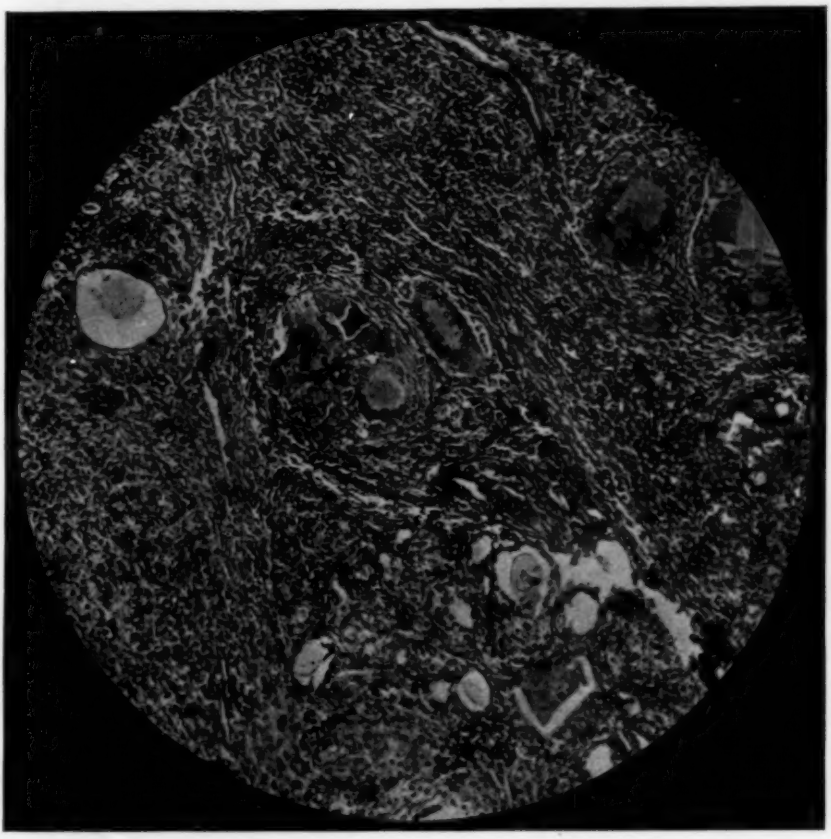

Fig. 2.—Case 3. Thyroid gland showing destruction of follicles and colloid and round cell infiltration and giant cell formation.

April 4, 1919.—A letter from patient bearing this date states that she has in general been well since her last visit; after May, 1916, she continued to take thyroid extract, 2½ grains daily.

She was married in September, 1916, and went west shortly afterward. During the next six months she gained considerable weight and reached 86 kg., but felt very well and had lots of energy. About a year later she felt dull and stupid, and says that she noticed that her hands and head were getting larger. She doubled the dose of thyroid and promptly became quite

normal again. She has continued on 5 grains daily, most of the time since then and except once when staying at a high altitude, has felt very well. Her weight is now 75 kg. She has had no children (Fig. 2).

Case 4.—*Myxedema.* (Lab. No. 5. Hospital No. 198640, E. M.) Mrs. R. A housewife, 41 years of age, first entered the hospital Nov. 12, 1914. Her family and past history were unimportant. For two or three years she had been getting sluggish mentally, and had felt chilly and objected seriously to cold weather. Her hair had grown coarse and her skin was dry, and she did not perspire at all. For four or five months she had noticed that her face and hands had become puffy.

Examination.—Physical examination showed the characteristic picture of myxedema—puffy face and definite thickening of the subcutaneous tissue. The skin was harsh and dry and the hair coarse and sparse. The thyroid was not enlarged. The blood, urine, blood pressure and Wassermann (blood) were negative. A roentgenogram of the head showed a normal sella turcica. The electrocardiogram showed a normal rhythm and an iso-electric "T" wave.

Nov. 13, 1914.—Basal metabolism was 13 per cent. below normal.

Nov. 14, 1914.—Basal metabolism was 25 per cent. below normal.

Nov. 15, 1914.—Patient started on thyroid extract, 1½ grains per day.

Nov. 17, 1914.—Thyroid extract was increased to 3 grains per day.

Nov. 23, 1914.—No physical sign of myxedema was in evidence. Basal metabolism was 16 per cent. below normal. The electrocardiogram showed a return of the normal "T" wave. Discharged on thyroid extract, 3 grains per day.

Feb. 9, 1915.—Patient called at the hospital to report. She had been perfectly well in feeling and appearance until one month previously, when her thyroid tablets ran out. She had taken none since, and in that time developed some slight dryness of the skin and began to feel cold again. A metabolism determination was not obtained, but she was started again on thyroid extract, this time on 1½ grains per day.

Case 5.—*Myxedema.* (Lab. No. 63. Hospital No. 807, C. C.). Mrs. G., a housewife, 63 years of age, seen in the consultation clinic for purposes of diagnosis, June 27, 1916 The history was that for eight or nine years she had been troubled by general weakness and by swelling of her ankles and eyelids; also with chilly sensations.

Examination.—Physical examination showed a woman with puffy face and hands, and with dry hair and dry, coarse skin. She was rather sluggish mentally. The urine was negative.

June 28, 1916.—A basal metabolism determination was made for differential diagnosis. It was found to be 18 per cent. below normal, and a diagnosis of myxedema was made. Her physician was advised to try thyroid administration.

April 1, 1919.—The patient did not again come under our observation, but on this date her physician wrote that the diagnosis had proved correct. He had found that thyroid extract, 2 grains per day, for a fortnight, alternating with a fortnight without the drug, kept her in perfect health. If she went longer than two weeks without thyroid extract the symptoms would recur.

Case 6.—*Carcinoma of Thyroid.* (Lab. No. 95. Hospital No. 211392, W. S.). Mr. B., a single man, 56 years of age, a watchmaker, entered the hospital, Oct. 30, 1916, with a history of having noted a swelling in his neck two years before, which had gradually been increasing in size. At about the same time he began to have a coarse tremor of the hands which had been growing worse and had become quite bothersome. Other symptoms referable to abnormal functionating of the thyroid gland were lacking. He had not lost weight.

Examination.—Physical examination showed a mass in the neck the size of a large orange, adherent to the trachea and moving with deglutition. It was twice as large on the left side as on the right and apparently involved the entire left lobe and isthmus and a portion of the right lobe of the thyroid.

It was hard and firm and not tender. The skin was somewhat dry and he had a very coarse tremor of the fingers, not at all like the tremor of exophthalmic goiter. He had no tachycardia and no eye signs. Laryngoscopy showed a restriction in motion of the left vocal cord, due probably to pressure on the left recurrent laryngeal nerve.

Oct. 31, 1916.—Basal metabolism was 19 per cent. below normal.

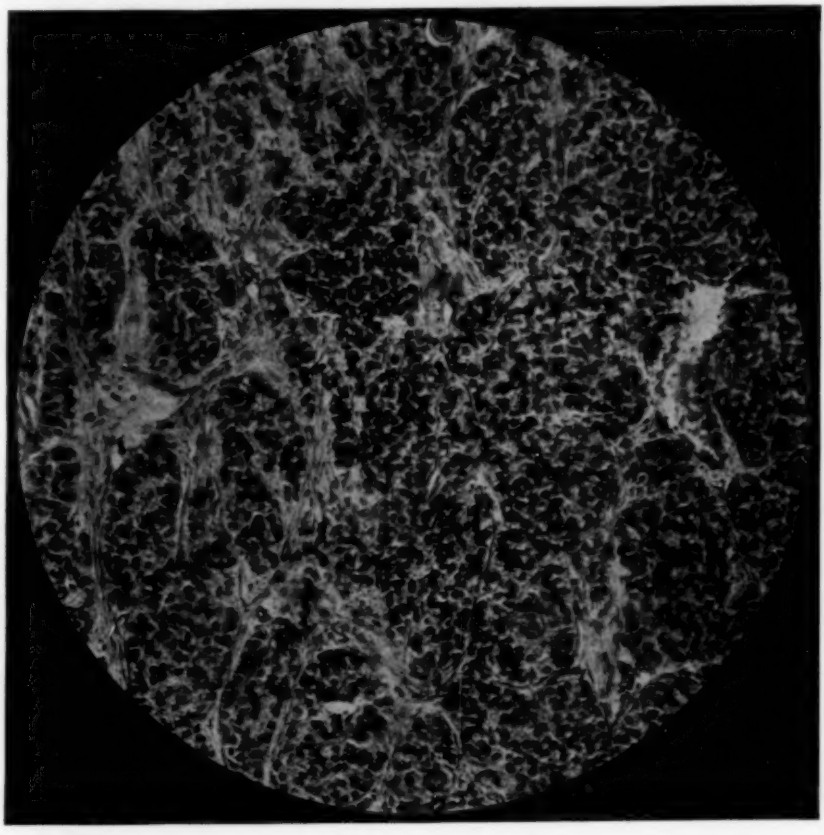

Fig. 3.—Case 6. Carcinoma of thyroid.

Operation.—Nov. 4, 1916, the patient was operated on under ether anesthesia, by Dr. G. W. W. Brewster. The tumor was removed and a small amount of normal thyroid tissue was left on the posterior portion of the capsule. The patient made a good ether recovery.

Pathologic Report.—A solid tumor, weighing 152 gm. and measuring 9.5 by 8 by 5 cm. It has a smooth red surface. Its section is reddish gray with areas of red and yellow softening and firm white bands. Microscopic examination shows solid columns of cells with small, irregular follicles which contain a dense eosin staining substance, suggesting colloid. The cells show con-

siderable atypicality. The stroma generally consists of narrow strands carrying blood vessels. Occasionally there are wide bands of fibrous tissue. There are numerous widely dilated, thin walled blood spaces. Occasional follicles are to be found lined with normal looking cells and filled with colloid like material. There were occasional mitotic figures. The anatomic diagnosis was carcinoma of the thyroid.

Nov. 13, 1916.—Discharged relieved.

Dec. 21, 1916.—Patient called at the hospital to report. He had been feeling well since his discharge, except for some weakness. The wound was well healed. He had the same coarse tremor; there was some slight evidence of hypothyroidism in that his skin was rather dry and he felt chilly and sweated almost not at all. The basal metabolism was 17 per cent. below normal.

Jan. 23, 1917.—He was seen in the out-patient department. His chief complaint was the tremor of the hands which interfered with his work.

April 15, 1919.—We learned that the patient was still alive but were able to get no information as to his present condition (Fig. 3).

DISCUSSION

The existence of a lowered respiratory metabolism in hypothyroidism and the ability of thyroid gland ingestion to raise it, has long been known. The work of Magnus-Levy in this field is by far the most comprehensive. This observer found in a normal woman a rise in the basal metabolism from the normal level to about 15 per cent. above normal after nineteen days thyroid ingestion, beginning with one tablet a day and working up to five tablets per day.[6] In a series of five cretins, three showed a reduction of from 40 to 50 per cent. and two of only 4 and 6 per cent. A case of cachexia strumipriva showed a reduction of 42 per cent.[7] Magnus-Levy used as a standard for comparison normal individuals of like height, weight and sex. This would be satisfactory except for the matter of age. One is at a loss to know with what to compare a cretin's metabolism. Shall we use that of a child of the same height, weight and sex, or shall we use the heat production per unit of surface area of an individual of the same sex and age? The reduction is quite obvious whichever standard is used, but in judging of the proper level to reach and maintain by thyroid administration we are at a loss. As a matter of fact, in the present investigation we have felt that it was probably more reasonable to use the latter criterion, namely, the metabolism per square meter of body surface of normal individuals of the same age and sex. The cretin of mature years, though of the stature of a child, differs from the child in the important respect that it has ceased growing, and hence it seems more reasonable to compare his or her metabolism with that of the adult. Furthermore, in speaking of variations from the normal we are erring on the safe side by using this criterion, for the differences

6. Magnus-Levy, A.: Ueber den respiratorischen Gaswechsel unter dem Einfluss der Thyreoidea, Berl. klin. Wchnschr. **32**:650, 1895.

7. Magnus-Levy, A.: Ueber Myxodem, Ztschr. f. klin. Med. **52**:201, 1904.

are less marked than they would be if we used the high metabolism of the normal child as a standard of comparison.

Magnus-Levy in his cretins and myxedema patients was able to produce a metabolic rise of anywhere from 17 to 72 per cent. by feeding thyroid preparations. Similarly, DuBois,[8] in his 36-year-old cretin, Benny L., raised the metabolism from about 20 per cent. below normal to normal for men of the same age, by giving thyroid extract, 3 grains per day, for three and one-half days.

More recently Janney[9] has made certain observations on the effect of Kendall's thyroid hormone in various types of thyroid disease. He did not determine the basal gaseous metabolism, but instead followed the nitrogen metabolism and drew his conclusions as to beneficial effects produced by the drug, from the improvement in the nitrogen balance. He found the optimal daily dose of hormone in cases of cretinism, to be 0.75 mg. which corresponds to 4 grains of thyroid tablets, and felt that larger doses are inadvisable.

Our observations of the basal metabolism in hypothyroidism are similar to those found in the literature. Our three myxedema patients before treatment showed variations of 33 per cent., 25 per cent. and 18 per cent. below the normal for their age and sex. Mrs. D. (Case 1), with the most marked grade of myxedema clinically showed the greatest reduction, and Mrs. G. (Case 5), with the mildest, the least. One cretin (Case 2) whose cretinism incidentally must be regarded as of a mild grade, showed a reduction of 23 per cent. below the normal for a woman of her age. The case of cachexia strumipriva (Case 3) is interesting, for after removal of the greater portion of her thyroid her metabolism was 14 per cent. below normal before any clinical manifestations of hypothyroidism were observed. The next observation in her case, while she showed a typical picture of myxedema, was 15 per cent. below normal. Unfortunately, she had been taking thyroid extract for eight days before this second observation was obtained. She reentered the hospital on the surgical service and had received 24 grains of thyroid extract before our attention was called to her case. Presumably her metabolism had been much lower preceding this course of thyroid extract. Similarly, in the case of Mr. B., with carcinoma of the thyroid (Case 6), there was a reduction of 19 per cent. in the metabolism before operation, and of 17 per cent. after operation on both occasions, without definite clinical evidence of hypothyroidism. From the metabolism results, however, it seems reason-

8. DuBois, E. F.: Metabolism in Exophthalmic Goiter, Clinical Calorimetry, XIV, Arch. Int. Med. **17**:915 (June) 1916.

9. Janey, N. W.: Studies in Thyroid Therapy, Arch. Int. Med. **22**:187 (Feb.) 1918.

able to assume that he was suffering from deficient thyroid secretion, which probably is explained by the fact that before operation his thyroid gland was largely replaced by tumor, and afterward the gland had been removed almost entirely.

As to the effect of thyroid therapy, we agree with Janney that small doses are better than large doses. In the case of Mrs. D. (Case 1) the metabolism was brought to normal and the symptoms of myxedema cleared up by a course of from 6 to 7½ grains of thyroid extract daily, over a period of about a month. Following this, after continuing with 1½ grains per day for a year, a course of 3 grains per day for two months raised her metabolism to 11 per cent. above the normal. However, when she was seen two years later, having been taking 1½ grains daily in the interim, her metabolism was 14 per cent. below normal. It seems likely in this case that the initial dose of thyroid was too large, not only because her metabolism rose above normal, but because between the third and fourth observations, while on 7½ grains of thyroid extract daily she suffered from considerable nausea and vomiting and general malaise. This was similar to DuBois' experience with the cretin, Benny L., who became nauseated and vomited while taking 3 grains per day. For a maintenance dose with Mrs. D. (Case 1), 3 grains apparently was too large, but 1½ grains was too small.

In the case of the cretin, Miss L. (Case 2), a total of 25½ grains of thyroid extract in a week restored the metabolism from 23 per cent. below normal to normal, without untoward results. Then a continuation of 1½ grains daily for several months served to keep her metabolism from 19 per cent. to 10 per cent. above normal. Following this, after a period of nine months without thyroid, it fell to 11 per cent. below normal. The initial dose of 4½ grains, therefore, was apparently not too large, but, on the other hand, the maintenance dose of 1½ grains per day was too large. Altogether, Miss L. was on thyroid therapy for fifteen months, and during that time she increased in height 2.3 cm.

In the case of Mrs. R. (Case 4) 21 grains of thyroid extract in eight days had had no noteworthy effect on the metabolism. Since her discharge from the hospital we have been unable to locate her.

With Mrs. G. (Case 5) we only obtained one observation, that before treatment was begun, but her doctor writes that 2 grains of thyroid extract per day half the time keeps her clinically normal.

It is interesting to contrast these results with those in the case of Miss N. (Case 3) with cachexia strumipriva. With her, initial doses of 3 grains promptly served to restore her metabolism to normal, but from her subsequent history a much larger dose (ultimately 5 grains

daily) has been necessary to keep her in normal health. This is not particularly remarkable, for while the thyroid glands of the cretin and myxedema patients may have had a certain functional activity, Miss N. was practically destitute of thyroid tissue, as only a few very small bits of normal gland were left at operation.

With a view to discovering any relationships which might exist between the metabolism level and the pulse rate, weight and respiratory quotient, we have plotted curves of these factors in the cases of Mrs. D. (Case 1) and Miss L. (Case 2). Between the metabolism level and the respiratory quotient there clearly is no relationship. Between the pulse curve and that of the metabolism level there is in both these patients a rough parallelism, but with definite discrepancies as well, as for example, in the fourth observation on Mrs. D. and the seventh on Miss L., in each of which instances the pulse was lower than in the preceding observation, while the metabolism was higher. Similarly between the weight curves and the metabolism curve there is sometimes a reciprocal relationship, but this is not sufficiently constant but that it might be accidental.

The clinical lessons to be drawn from these studies we believe to be as follows: First, that the level of the basal metabolism is a better index of the degree of thyroid lack than is the clinical picture, and second, that the proper dosage of thyroid preparations can be far more accurately gaged by following the effect on the metabolism than from the appearance and symptoms of the patient. The aim should be to bring the metabolism to the normal level and then find the minimum dose that will keep it there. Janney's method of using the nitrogen balance as a criterion is no doubt good, but it requires a metabolism ward and considerable time and care to make such studies. The basal metabolism on the other hand can be determined quite easily and requires not more than an hour's time. The procedure is especially easy if Benedict's new portable apparatus is used.[10]

We should agree with Janney that large doses of thyroid extract are to be avoided. For the initial treatment 3 grains per day should be sufficient to bring the metabolism to normal, and after the normal level has been reached from 1 to 2 grains may be required to keep it there. The proper maintenance dose will vary among different patients, and should be decided by metabolism determinations.

The importance of following the metabolism in cases of hypothyroidism is emphasized by the fact that our results show that a lowered metabolism, and hence presumably a state of hypothyroidism,

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10. Benedict, F. G.: Portable Respiration Apparatus for Clinical Use, Boston M. & S. J. **178**:667 (May 16) 1918.

may occur without clinical manifestations and also by the fact that by thyroid therapy the metabolism can be raised above normal without clinical evidence of thyrotoxicosis.

SUMMARY AND CONCLUSIONS

1. Basal metabolism determinations are reported in three untreated cases of myxedema. All showed a definite reduction below that of normal individuals of the same age and sex.

2. Similarly the basal metabolism in an untreated cretin and in a case of cachexia strumipriva, showed a marked reduction. In the latter case the fall in metabolism antedated the clinical appearance of hypothyroidism.

3. In a case of carcinoma of the thyroid a moderate reduction in basal metabolism was found, both before and after thyroidectomy without clinical evidence of hypothyroidism.

4. The metabolism of all patients studied during thyroid therapy was readily brought to normal, or above, by the administration of thyroid extract.

5. The determination of the basal metabolism forms a sound and convenient method for governing the dosage of thyroid preparations in cases of hypothyroidism, and furnishes a far better guide in this respect than does the clinical picture. It is also of value as a means of differential diagnosis in obscure cases.

6. In the treatment of hypothyroidism doses of from 3 to 4 grains of thyroid extract daily should be ample to bring the metabolism to normal in two or three weeks, and doses of from 1 to 2 grains daily should usually be sufficient to keep it there.

7. Cases of cachexia strumipriva may require larger maintenance doses than those of spontaneous hypothyroidism.

15 Chestnut Street.

THE RELATION OF NEUROCIRCULATORY ASTHENIA TO HYPERTHYROIDISM AS DETERMINED BY THE EFFECTS OF THE INJECTION OF EPINEPHRIN

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Many of the symptoms of neurocirculatory asthenia are so similar to those found in hyperthyroidism, that the theory that this condition is a latent or a very mild thyrotoxicosis has often been advanced. Goetsch has employed epinephrin, given subcutaneously, as a test for latent hyperthyroidism. The detailed technic employed is described by Peabody[1] in a report on the effects of epinephrin on soldiers with irritable heart. I performed the same test in a series of twenty-one consecutive cases in June, 1918,[2] and it is these that I wish to report.

The test, in short, consists of subcutaneous injection of 0.5 c.c. of a 1:1,000 epinephrin solution, with subsequent observations of the pulse rate, blood pressure, tremor, nervousness and throbbing of the blood vessels. Since the systolic blood pressure of these patients is so very labile, they are allowed to rest on a bed until the blood pressure readings have become constant. A rise in pulse rate and blood pressure and an augmentation of the nervous phenomena indicates a positive reaction. A normal individual shows none of these changes. An illustrative protocol may be cited (Table 1).

TABLE 1.—FINDINGS IN ONE CASE FOLLOWING THE INJECTION OF EPINEPHRIN

Time	Pulse	Blood Pressure	Nervousness	Tremor	Cold Hands	Throbbing of Neck Vessels	Remarks
10:12	92	116/65	Slight	Slight	Slight	Slight	
10:18	84	118/65					
10:18*							
10:21	120	144/70	++	++	Slight	+	
10:24	104	144/64	.....	.....	+	+	Vertigo
10:27	88	132/58					
10:32	92	132/62	+++	++	+	+	Respiration 32; deep
10:42	88	136/70	+++	+++	+	+	Patient very restless
10:52	84	130/74	++	++	++		
11:03	88	142/72	++	++	++	+	
11:13	84	132/70	+	+	+	+	
11:23	88	130/75	Slight	Slight	Slight	Slight	Vertigo
11:33	88	136/70	.....	.....	.....	.....	Headache

* Epinephrin 1:1,000, 0.5 c.c. subcutaneously.

1. Peabody, F. W., et al.: Effects of the Injection of Epinephrin in Soldiers with "Irritable Heart," J. A. M. A. **71**:1912 (Dec. 7) 1918.

2. Boas, Ernst P.: On the Nature of Neurocirculatory Asthenia, Report to Surgeon-General, June 27, 1918.

Various subjective symptoms were complained of by the patients who gave a positive reaction. Chief among these were precordial pain, vertigo, headache, epigastric distress and nausea. Two of the men became very restless, tossing about on the bed with rapid, deep, at times gasping respirations. Four of the patients with negative reactions complained of slight vertigo.

TABLE 2.—SUMMARY OF RESULTS OF TEST IN TWENTY-ONE CASES

Case No.	Thyroid	Family History of Nervousness	Cardiac Symptoms	Gastro-intestinal Symptoms	Bodily Type	Reaction
1	Isthmus palpable	Mother; brother	+	+	Erethic	+
2	Not palpable	Mother; sister	+	+	Erethic	+
3	Not palpable	Mother; brother	+	+	Ptotic	+
4	Not palpable	Mother; two brothers	+	+	Ptotic	+
5	Not palpable	Mother; brother	+	—	?	+
6	Not palpable	Brother	+	—	Stocky	+
7	Isthmus and left lobe	Negative	+	—	Erethic	—
8	Isthmus just palpable	Mother; father	+	—	Erethic	—
9	Isthmus large	Mother; two sisters	+	+	Normal	—
10	Not palpable	Negative	+	Very slight	Erethic	—
11	Not palpable	Mother	+	+	Ptotic	—
12	Not palpable	Mother; sister	+	Slight	Erethic	—
13	Not palpable	Father; mother; three brothers; three sisters	+	+	Ptotic	—
14	Not palpable	Father; sister	+	+	Ptotic	—
15	Not palpable	Mother; sister; brother	+	—	Ptotic	—
16	Not palpable	Negative	+	—	Stocky	—
17	Not palpable	Brother	+	—	Ptotic	—
18	Not palpable	Mother	+	—	Normal	—
19	Not palpable	Father	+	—	Ptotic	—
20	Not palpable	Mother	+	?	Normal	—
21	Not palpable	Negative	+	—	Normal	—

It is noteworthy that only four of the patients had palpable thyroids and that only one of these gave a positive reaction. None of the men had exophthalmos, nor any other eye signs that are seen in exophthalmic goiter. The bodily type of the individual seemed to have no influence on the result of the test. By the erethic type are meant men of good build, with high color, who have marked vasomotor instability, manifested by frequent flushing, vertigo on change of posture, and headaches. By the ptotic type are meant men who conform to what is often known as the tubercular habitus. All but four of the men give a family history of "nervousness." Nervousness as used by these patients in describing the symptoms of their relatives usually means a nervous instability similar to that which they exhibit.[3] Four out of six of the positive cases have gastro-intestinal symptoms of a func-

3. Robey, W. H., Jr., and Boas, E. P.: Neurocirculatory Asthenia, J. A. M. A. **71**:525 (Aug. 17) 1918. Oppenheimer, B. S., and Rothschild, M. A.: The Psychoneurotic Factor in the Irritable Heart of Soldiers, J. A. M. A. **70**:1919 (June 22) 1918.

tional nature; while only six out of fifteen of the negative cases show this association. However, the series is too small to attach any significance to this fact. Thus an analysis of the epinephrin reaction in this group of cases shows that it is impossible to predict from any of the criteria that we have at present, whether or not any particular case of neurocirculatory asthenia is sensitive to epinephrin or not.

In a series of sixty-five cases, Peabody found positive reactions in 60 per cent. of the cases. In my smaller series only 28.6 per cent. of the men reacted positively. Granted that the test gives an indication of latent hyperthyroidism, it is clear that all cases of neurocirculatory asthenia are not to be explained on this basis. Even in the positive cases the thyroid hyperfunctioning may be only a symptom and not a cause of the condition. Addis and Kerr,[4] in a study of the frequency with which the symptoms of neurocirculatory asthenia occur in recruits with and without thyroid enlargement, found that there was no relation between thyroid enlargement and the occurrence of the syndrome. Lewis[5] found palpable enlargement of the thyroid in only 4 per cent. of his cases of irritable heart. Furthermore, as has been pointed out before,[3, 6] the typical eye signs of exophthalmic goiter are rarely, if ever, found in patients with neurocirculatory asthenia. The tremor in the latter disease is much coarser, and finally, in spite of the fact that the symptoms may exist for years, cardiac hypertrophy, such as is found in goiter, is never seen in these men with "irritable heart." Undoubtedly, different causes contribute to the appearance of the symptom-complex. Further study, particularly with a view to grouping the cases according to whether the symptoms are chiefly cardiovascular, gastro-intestinal, or mental is essential to shed further light on the true nature of this common but baffling condition.

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4. Addis, T., and Kerr, W. J.: Relative Frequency in Recruits With and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia, Arch. Int. Med. **23**:316 (March) 1919.

5. Lewis, T.: Reports on Soldiers Returned as Cases of "Disordered Action of the Heart," Medical Research Committee, Special Report Series, No. 8, London, 1917.

6. Cohn, A. E.: The Effort Syndrome, J. A. M. A. **71**:3132 (Dec. 25) 1918.

THE SIGNIFICANCE OF ABNORMALITIES IN THE FORM OF THE ELECTROCARDIOGRAM *

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Much interest has recently been shown in the relation of changes in the form of the electrocardiogram to disturbances of the myocardium. This interest is centered for the most part about changes in the form of the ventricular portion of the electrocardiogram, which have been interpreted as indicative of faulty conduction of the cardiac impulse through the ventricles. The abnormal form of the electrocardiogram, to which attention is directed in this paper, consists in a prolongation of the initial group of waves of the ventricular portion, the so-called Q-R-S group, with notching or splitting of the main wave, the R wave. A consideration of this portion of the electrocardiogram is important, as it renders valuable information concerning the state of the myocardium, and has proved of distinct value in determining the diagnosis and prognosis in numerous cases of heart disease.

It is a well established fact that the electrical phenomenon accompanying cardiac activity, which is expressed by the electrocardiogram, begins before the actual contraction of the heart muscle, and the first series of waves constituting the ventricular portion of the electrocardiogram represents, in part, the spread of the cardiac impulse into and through the ventricles. A disturbance in the passage of cardiac impulse along the intraventricular conducting system and through the ventricular musculature causes a change in the form of the first portion of the ventricular curve. The prolongation of the Q-R-S group indicates that the time required for the complete activation of the ventricles is lengthened, and the notching probably indicates that the activation of the various portions of the ventricles is not taking place in its proper sequence. This interpretation of the type of abnormal electrocardigram which has been mentioned is generally accepted. The purpose of this paper is to present some facts which apparently throw light on the mechanism by which the conduction into and through the ventricles is sometimes disturbed, and an interpretation of the abnormal electrocardiogram is offered which differs from that which has been generally expressed.

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In a paper which I published in 1916,[1] electrocardiograms were reproduced which demonstrated that the type of abnormal electrocardiogram which is here under discussion may result when the stimulus of the heart beat reaches the ventricles before they have fully recovered from previous activity and when they are in a state which may be conveniently termed functional fatigue. It was pointed out in this paper that under these circumstances the disturbance of the intravenous conduction is dependent on the fact that an insufficient time has elapsed for the recovery of the ventricles and the curves reproduced show that when a sufficient length of time has elapsed the following electrocardiogram has a form which is much nearer that yielded by the normal heart. This is especially well seen in a record from a case of sino-auricular block in which an idioventricular contraction usually occurs during the latter part of the pause caused by the block. This idioventricular contraction precedes by a short interval the auricular beat, which sends down a stimulus to the ventricles, stimulating them soon after the completion of the idioventricular contraction. The interval of time elapsing between the idioventricular contraction and the stimulation of the ventricles by the impulse sent down by the auricular contraction varies, and the form of the ventricular complex produced by the second ventricular activity also varies in form. A study of a large series of records from this case shows that the form of the complex yielded by the second ventricular contraction bears a direct relationship to the period of rest that precedes it. When the period of rest is very short the ventricles fail to respond to the impulse descending from the auricles. When the period of rest is somewhat longer, the ventricles respond, but yield a complex with a much prolonged Q-R-S group and with well defined notching of the R wave. When the period of rest is still further prolonged the ventricular complex approaches the normal complex in form. This is shown in Figure 1 of the previous paper.

The records of this case demonstrate, therefore, that so-called functional fatigue may be responsible for the abnormal form of the ventricular complex under discussion, and in this instance an anatomic lesion can hardly be considered as playing a rôle in its production.

In the paper that has been mentioned records of a case of auricular fibrillation were reproduced in which the same abnormalities of form are seen in the ventricular portion of the electrocardiogram whenever the diastolic pause preceding the ventricular contraction is relatively short, while following longer pauses the ventricular complex assumes

1. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916.

a form much nearer the normal. The interpretation seems justified that the disturbance in conduction through the ventricles in this case is dependent on lack of time for recovery, and that when sufficient time elapses between beats, intraventricular conduction apparently takes place at a relatively normal rate and in a relatively normal manner. (Figs. 4 and 5 of the previous paper.)

The evidence of these two cases and others reported with them has led to the belief that in cases in which the ventricular complexes constantly show certain abnormal forms there may be functional changes in the heart which prevent the normal recovery of intraventricular conduction during diastole. This explanation for the cause of the abnormalities of the electrocardiogram under discussion has not, however, been emphasized by those who have since published papers on this subject. Thus Oppenheimer and Rothschild[2] have attempted to correlate gross and histologic changes in the hearts of several patients with the abnormal form of electrocardiogram without considering the possibility that physiologic rather than anatomic changes might be responsible for the altered form of the electrocardiograms. Although they mention the cases showing temporary changes in the electrocardiograms, they seem to consider that they belong to another type of case from those which they describe. This division of the cases does not seem to me to be justified.

Following this paper by Oppenheimer and Rothschild there seems to have been a general acceptance in this country of the idea, either stated or implied, that abnormal forms of electrocardiograms are indicative of intraventricular block caused by localized subendocardial lesions. This is to be noted in the papers of Blackford, Willius and Haines,[3] Neuhof,[4] Carter[5] and Willius.[6] Wedd,[7] whose paper deals with less pronounced changes in the form of the electrocardiogram, recognizes, however, the possibility of functional derangement of intraventricular conduction without localized lesions in the conducting system. Willius goes so far as to state that "arborization block or impaired intraventricular conduction is dependent on graphic records

2. Oppenheimer, B. S., and Rothchild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

3. Blackford, J. M., Willius, F. A., and Haines, L. B.: Operative Risk in Cardiac Disease, J. A. M. A. **69**:2011 (Dec. 15) 1917.

4. Neuhof, S.: The Clinical Significance of the Abnormally Wide Ventricular Deviation in the Electrocardiogram, Arch. Int. Med. **22**:45 (July) 1918.

5. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrio-Ventricular Bundle Branches and Their Terminal Arborization, Arch. Int. Med. **22**:331 (Sept.) 1918.

6. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

7. Wedd, A. M.: The Clinical Significance of Slight Notching of the R Wave of the Electrocardiogram, Arch. Int. Med. **23**:515 (April) 1919.

for its recognition. It is now generally accepted to indicate disease of the subendocardial myocardium and evidence of serious functional cardiac disturbance. The involvement occurs in the subendocardial or Perkinje plexus." This statement is made in spite of the fact that the postmortem examination of five hearts revealed no definite localizing lesions, but rather diffuse degenerative processes involving the myocardium.

Carter has reported a case yielding abnormal electrocardiograms in which a very careful histologic study of the subendocardial structures was made. He considers that there existed a causal relation between the abnormal electrocardiograms and the sclerosis that we found in the atrioventricular bundle branches and their terminal arborizations. In this case the explanation of the abnormal electrocardiograms seems well grounded, although not definitely proved. There was found a discrepancy between the amount and position of the sclerotic changes in the ventricular conducting system and the anticipated form of the electrocardiogram, suggesting that some other factor than the anatomic lesion may have been operative.

Fridericia and Møller[8] also report a case showing abnormal electrocardiograms in which there was an extensive lesion in the intraventricular system causing, the authors consider, intraventricular block.

I have recently had an opportunity of studying a case which seems to throw some new light on the causation of the abnormal form of electrocardiograms, which I wish to report before considering the underlying causes of the disturbance of intraventricular conduction.

CASE REPORT

A man, 63 years of age, a telegraph operator, entered the hospital with severe symptoms of cardiac decompensation, showing marked dyspnea, edema of the extremities and cyanosis. His history revealed no definite etiology, but there was an unsubstantiated history of syphilis. He had had cardiac symptoms, especially palpitation, for about a year, and had dyspnea for six months, with frequent attacks of nocturnal dyspnea. From the examination a diagnosis of arterial sclerosis, chronic myocarditis, auricular fibrillation and mitral insufficiency were made. Electrocardiograms obtained May 10, 1917, showed the ventricular rate to be 135 per minute, and the form of the ventricular portion was abnormal in all leads, the initial group of waves being prolonged to 0.170 to 0.180 second (maximum normal = 0.100 sec.) and definite notching was present. The form of the electrocardiogram suggested right branch bundle block, but was not typical, and indicated a high degree of derangement in the intraventricular conducting system (Fig. 1).

This patient was given a single dose of a standardized tincture of digitalis, 6 c.c., the dose being smaller than that usually administered in cases of auricular fibrillation in this clinic, because of a history of having taken the drug in small doses up to the time of admission to the hospital. The patient responded

8. Fridericia and Møller, P.: Et Tilfaelde af Myocarditis, lokaliseret til septum Ventriculorum, med ejendommelize abnormiter; Elaktrokaardiogrammet, Hospitalstid. **60**:573 (June 13) 1917; **60**:597 (June 20) 1917.

remarkably well to the drug and electrocardiograms obtained two days later showed a ventricular rate of 69 per minute. The form of the ventricular complexes was strikingly changed. The initial group of waves had a duration of from 0.92 to 0.10 second, and the notching of the main wave had almost entirely disappeared (Fig. 2). The clinical improvement was also striking. No more digitalis was administered at this time and the ventricular rate gradually increased. Electrocardiograms obtained May 13 and May 15, showed a rate of 85 per minute, with increased arrhythmia (Fig. 3). In the records the ventricular complexes have distinctly more notching and prolongation of the initial group of waves than that obtained when the ventricular rate was 69 per minute. A feature of these records is the definite abnormality of form seen in the complexes yielded by the ventricular contractions which are preceded by short diastolic periods. Under these conditions the complexes have a form approaching that seen when the heart was beating at a rate of 135 per minute.

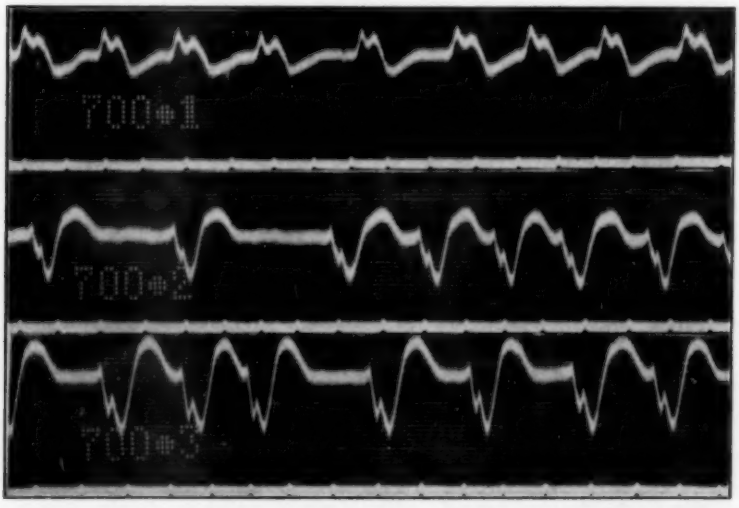

Fig. 1.—Electrocardiogram, three usual leads, obtained May 10, 1917, when patient first entered the hospital. Ventricular rate, 135 per minute. Initial group of waves of ventricular complex from 0.170 to 0.180 second in duration.

The administration of digitalis again slowed the heart and caused a disappearance of the electrocardiographic evidence of disturbance of intraventricular conduction. Cardiac efficiency became much improved and the patient left the hospital with instructions to use the tincture of digitalis constantly. These instructions were not carried out, however, and the patient returned six weeks later with slight signs of cardiac inefficiency and with a ventricular rate of from 144 to 158 beats per minute. At this time, however, the electrocardiograms failed to reveal any prolongation of the initial waves of the ventricular complexes, and only slight notching was present (Fig. 4). In other words, at this time, in spite of a higher ventricular rate than that first seen, there was practically no evidence of a disturbance of intraventricular conduction. The use of the tincture of digitalis again slowed the heart, and a record obtained one month after the second admission showed a ventricular rate of 61 beats per minute, with practically no change in the form of the electrocardiograms.

It is difficult to conceive how the disturbance in the intraventricular conduction which was evidently present in this case when first observed could have been caused by an anatomical lesion involving the subendocardial tissues and the arborization of the ventricular conductory system, because of its rapid disappearance when the heart rate became slowed by digitalis. The fact that the disturbance of intraventricular conduction, the so-called arborization block, did not return later with the increase in ventricular rate also indicates that some improvement in the physiologic processes of the heart had occurred during the period of treatment.

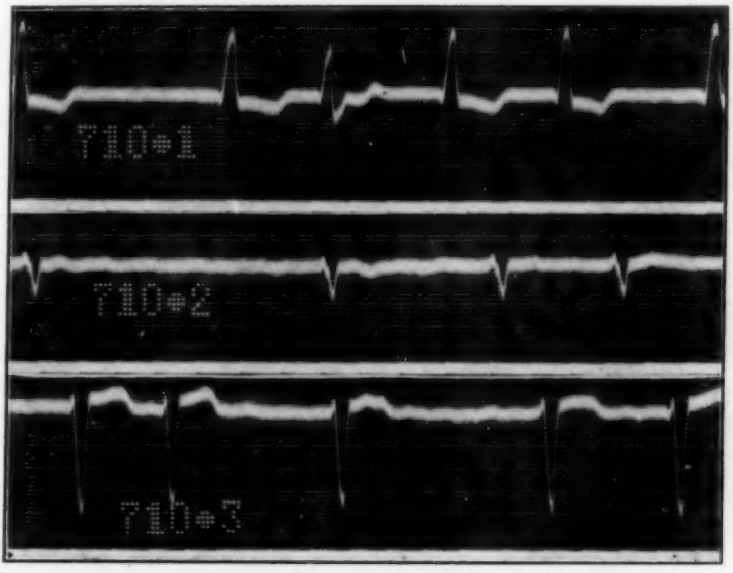

Fig. 2.—Electrocardiogram obtained May 12, 1917, after a single dose of digitalis had been given. Ventricular rate 69 per minute. Striking change in form of complexes. Initial group of waves of ventricular complex from 0.092 to 0.100 second in duration.

A consideration of this case as well as of those that have already been reported and reviewed brings out the necessity for another explanation than that which had been offered by Oppenheimer and Rothschild and others to account for the abnormalities in the form of the electrocardiograms seen in these cases.

The term functional fatigue has already been used to account for the derangement of intraventricular conduction. Of course, a recognized change in structure may bear a causative relation to a derange-

ment in a physiologic process, but in the light of the cases that I have reported this association can by no means be taken for granted, and other so-called physiologic factors must come into play in these cases.

I wish to discuss briefly the possible physiologic factors that seem to me likely to play a rôle in the production of disturbances in intraventricular conduction, and which in turn may be worthy of consideration as a factor in the production of cardiac inefficiency in cases of heart disease.

In the cases under consideration an improvement in the state of the intraventricular conduction takes place during the diastolic periods when the heart is at rest. But instances are seen when the diastolic period is not long enough to allow complete recovery, and in the case reported in this paper the recovery of intraventricular conduction is slower at

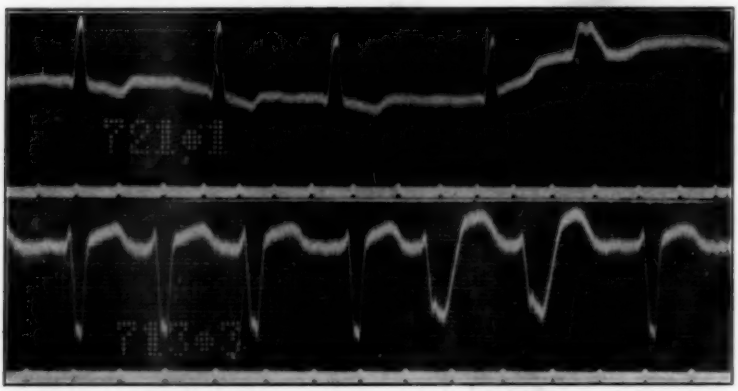

Fig. 3.—Electrocardiograms obtained May 13 and May 15, 1917. Ventricular rate, 85 per minute. The form of the ventricular complexes and the duration of the initial group of waves depend on the length of the preceding diastole. First and third leads are shown.

one time than at another. It may be inferred from these observations that certain metabolic processes occur during ventricular activity which affect the function of the conducting mechanism, and that a definite time is required for the recovery of the ventricles before the conducting of the cardiac impulse proceeds through them in a normal manner. The length of time required for this recovery may be increased distinctly in damaged hearts, and under certain conditions the diastolic rest may be continually insufficient to allow complete recovery of the intraventricular conducting system. This is apparently the cause of the abnormal electrocardiograms shown in Figure 1. Figure 3 shows, however, that the degree of recovery of the conducting system is

dependent on the length of the cardiac rest afforded by the diastolic period.

I wish to suggest that the derangement of intraventricular conduction which is indicated by the abnormal form of the electrocardiogram may be caused in these cases by the presence of acid metabolites, and that these acid metabolites are present in increased amounts when there is a deficient supply of oxygen to the tissues involved.

The basis for this explanation is the work of Fletcher and Hopkins[9] on the effect of diminished oxygen supply on muscle activity and the work of Mines[10] and of Burridge[11] on the effects of changes in hydrogen ion concentration on conduction through the ventricles.

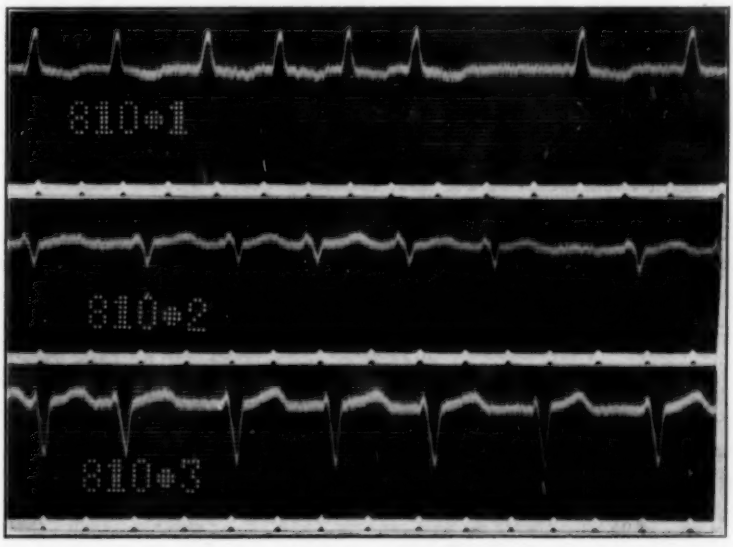

Fig. 4.—Electrocardiogram obtained June 29, 1917. The ventricular rate is 158 per minute, but the abnormalities of the ventricular complexes previously seen do not occur.

Fletcher and Hopkins have carried out an investigation on lactic acid in amphibian muscle, and state that there is a large body of well-known evidence which indicates that the disposal of acid products — whatever the site of it may be — is most efficient when conditions for

9. Fletcher and Hopkins: Lactic Acid in Amphibian Muscle, J. Physiol. **35**:247, 1907.

10. Mines: On Dynamic Equilibrium in the Heart, J. Physiol. **46**:349, 1913.

11. Burridge: Propagation of Contraction in the Frog's Heart, J. Physiol. **45**:6, 1912.

oxidative processes are most favorable, and that it is incomplete when these conditions are unfavorable. Their experiments show that the lactic acid formed in muscle follows this rule, and its disappearance from muscle is dependent on the oxygen supply.

With these facts in mind, it is not difficult to conceive that acid metabolites tend to accumulate in the heart muscle when the oxygen supply is insufficient to meet the demands of the rapidly beating heart. In a number of the hearts showing delayed intraventricular conduction marked sclerosis of the coronary arteries have been observed, notably in the series of Oppenheimer and Rothschild[2] in which twelve of the fourteen hearts examined postmortem showed well defined coronary artery sclerosis. This lesion may, therefore, be considered responsible for an inadequate oxygen supply to the heart muscle, which results in an excessive production of acid metabolites.

Burridge[11] has shown that the addition of acid to the fluid with which the frog's heart was perfused caused a delay in the conduction of the impulse. He states further that if sufficient acid were added to cause the heart to stop beating, sodium bicarbonate neutralization brought back the beat, but with markedly delayed conduction of the impulse through the ventricle. Mines[10] has used these experiments to account for certain changes in the electrocardiogram which result from increased frequency of the heart beat which he believes may lead to changes in the hydrogen ion concentration in some region of the muscle. If these experiments can be considered as holding good for the chemical changes that occur during the cardiac action of the human heart, they seem to justify the hypothesis that any change which diminishes the oxygen supply to the heart muscle will favor the accumulation of acid metabolites and consequently cause a derangement in the propagation of the cardiac impulse through the ventricles. This derangement would become apparent whenever the diastolic rest is of insufficient duration to allow the removal of the acid metabolites from the ventricular structures. Sclerosis of the coronary arteries would furnish the condition for the increased production of acid metabolites and also tend to delay their removal. Myocardial lesions, such as a fibrosis, would perhaps also tend to produce these effects by lessening the efficiency of the blood supply to the ventricular structures.

It should be stated that an objection to the foregoing hypothesis may be raised in that there is no evidence that acid metabolites are produced by the activity of the conducting system. Erlanger[12] was unable to discover the production of acid in the conducting system as a result of its activity. The effect of acid produced in the muscle on conduction is therefore open to question.

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12. Erlanger, J.: Personal communication.

SUMMARY

Certain abnormalities in the form of the electrocardiogram are recognized as evidence of faulty conduction of the cardiac impulse through the ventricles. These abnormalities consist of a prolongation of the time required to complete the first series of waves, the Q-R-S group of the ventricular part of the electrocardiogram and notching of the main wave of the group. An attempt has been made by several writers to associate faulty conduction of the cardiac impulse within the ventricles with anatomical lesions involving the intraventricular conducting system. This association may be correctly assumed in some cases, but in this paper cases are reported which seem to prove that faulty conduction through the ventricles may depend on what has been termed "functional fatigue." Examples are cited in which derangement of ventricular conduction has resulted from lack of time for conduction recovery after a ventricular contraction. In the case reported distinct improvement in ventricular conduction followed slowing of the heart rate, when longer diastolic pauses were present. The rate of recovery of conduction was observed also in this case to become more rapid with improved circulatory efficiency.

The hypothesis is advanced that in the cases referred to in this paper the disturbance of intraventricular conduction is the result of the presence of acid metabolites in the ventricular structures, and that sclerosis of the coronary arteries and perhaps other lesions causing an insufficient blood supply to the ventricles are responsible for the presence of the acid metabolites, as it has been shown that these accumulate whenever the oxygen supply to muscle is inadequate. This hypothesis renders an anatomic lesion in the subendocardial structures unnecessary to account for the disturbance of the intraventricular conduction, although the effect of acid produced in the muscle on conduction is still open to question.

THE USE OF LABORATORY METHODS IN THE DIAGNOSIS OF EARLY HYPERTHYROIDISM

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The following study was prompted by the desire to discover means of differentiatng early or borderline hyperthyroidism from functional cardiac disorder through the aid of the laboratory.

The recognized laboratory test for hyperthyroidism is that for basal metabolism as developed by Rubner, Magnus-Levy, Salomon, DuBois, Henderson, Peabody and others. The respiratory gas interchange as estimated by this test, shows an increase of from 50 to 80 per cent. of oxygen consumed in several cases, and from 20 to 50 per cent. increase in mild to moderately severe cases of hyperfunctional activity of the thyroid.

Such an apparatus was not available for the present study. There are still but few in use in this country. Either the Benedict or a modified Haldane is the apparatus of choice. Both require quite a measure of special skill in their manipulation.

Other more simple laboratory tests were applied: The sugar tolerance test;[1] the epinephrin test;[2] tests for nitrogen loss; tests for acidosis.[3] These tests can readily be learned by every clinician interested, and may be performed in a small office laboratory, either by the physician himself or his assistant. The epinephrin test is carried out at the bedside or in the physician's office.

The work recorded in this paper was completed at the Base Hospital, Camp Dix, N. J. As regards the study of nitrogen elimination, I would have wished that facilities and assistance had permitted more exact metabolic studies, especially in weighing diets, and estimating nitrogen intake. Later studies will better satisfy research requirements. For most exact estimations for acidosis, Van Slyke's plasma CO_2 test[3] gives the most reliable and direct results. The tests reported here: for total acidity of urine, sodium bicarbonate tolerance and urinary ammonia are also reliable as an indirect measure of blood alkali reserve. The group of patients studied were admitted to the

1. Janney, N. W., and Isaacson, V. I.: A Blood Sugar Test, J. A. M. A. **70**:1131 (April 20) 1918.

2. Goetsch, Emil: Newer Methods in the Diagnosis of Thyroid Disorders: Pathologic and Clinical, New York State J. M. **18**:259 (July) 1918.

3. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis, J. Biol. Chem. **30**:289 (June) 1917.

cardiovascular service for observation, diagnosis and treatment, later to be discharged or transferred. Seven patients, from clinical symptoms, undoubtedly had exophthalmic goiter. About twenty other patients were studied at the same time with the goiter patients. Some of the twenty, by symptoms alone, could most readily be said to have a functional cardiac disorder. Both groups were studied by means

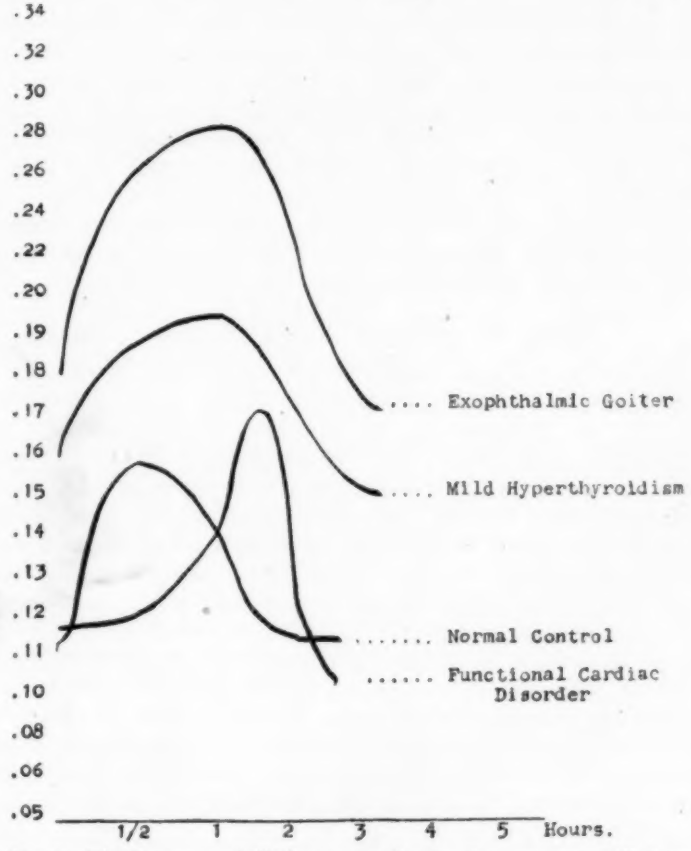

Fig. 1.—Blood sugar assimilation curves for the three groups studied, compared with the normal curve.

of the laboratory methods mentioned above. When results were compared, four or five from the larger group are called in this paper early or mild hyperthyroidism.

The cases diagnosed by laboratory study as hyperthyroidism, presented symptoms suggesting a derangement of the sympathetic nervous

system, namely: tremors, sweating, nausea, insomnia, nervousness and headaches. The characteristic symptoms of the patients remaining in the functional cardiac disorder group directed attention to the heart and circulatory system, namely: precordial pain (especially), dyspnea on exertion, tachycardia, syncope, cyanosis and exhaustion.

It was found that a palpable and even a moderately enlarged thyroid may be present in both groups. The laboratory tests seemed to provide a means of separating the hyperactive thyroid from the simple hypertrophied gland found associated with functional cardiac disorder.

I am aware of the intimate correlation and interaction of the internal secretory glands and that metabolic and functional derangements pointing to a dysfunction of one endocrine system does not preclude hormone disorders of other glands. Nevertheless, any effort to differentiate true hyperthyroidism from true cardiac neurosis, is of value not only from a therapeutic standpoint, but equally from a preventive one—to institute prophylactic treatment before exophthalmus, thyroid and myocardial injuries become permanent.

I. RESULTS OF THE BLOOD SUGAR TOLERANCE TEST

The results are to be studied in relation to normal blood sugar tolerance figures. The average blood sugar fasting level is represented by 0.095 per cent. glucose concentration. Normal figures range between 0.07 and 0.12 per cent. concentration; 0.18 per cent. concentration is the average threshold level for blood sugar, above which point sugar often overflows into the urine in amounts large enough to be detected by the ordinary qualitative sugar tests. In but few of the cases here recorded could definite positive tests for glycosuria be reported. Duplicate tests were often made in the blood sugar estimations, and the average recorded; especially was this done in estimating the fasting level, prior to sugar ingestion. In the tolerance tests here recorded, when the blood sugar curve, following the ingestion of a 40 per cent. solution of glucose or of sucrose, 1.75 gm. per kilogram of weight, extends over two or two and one-half hours before returning to or below the initial fasting level, the assimilation for glucose is said to be delayed. When glycosuria results, the tolerance for sugar is said to be decreased.

Table 1 gives the results of the sugar tolerance test in seven cases of exophthalmic goiter. With two exceptions, the blood fasting level was high, that is, hyperglycemia was present in five of the seven patients. The assimilation curves were prolonged, with one exception, over two and one-half hours, and the peaks of the curves were characteristically high. Two of the five cases in which the urine was examined, at hourly intervals, following the sugar ingestion, showed decreased tolerance or glycosuria.

TABLE 1.—Blood Sugar Tests in Exophthalmic Goiter

Case	Fasting Level, per Cent.	After Sugar Ingestion							
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.
H. T.	0.085	0.176	0.184	0.172	0.160	0.150	0.174	0.160	0.140
R. H.	0.154	0.150	0.182	0.184	0.180	0.162	.....	0.146	.....
B. C.	0.140	0.190	.....	.....	0.176	0.145	.....	.....	.....
R. B.	0.093	0.100	0.222	0.168	0.156	0.152	0.146	.....	0.140
B. E.	0.127	0.134	0.162	0.200	0.164	0.166	0.145	0.135	0.135
W. J.	0.142	0.230	0.188	0.174	0.188	0.142	0.142	.....	.....
D. G.	0.180	0.202	0.282	0.230	0.216	0.193	0.170	0.170	.....

TABLE 2.—Blood Sugar Tests in Early Hyperthyroidism

Case	Fasting Level, per Cent.	After Sugar Ingestion							
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.
L. C.	0.142	0.160	0.168	0.190	.....	0.160	0.160	0.138	0.122
L. C.	0.160	.....	0.195	.....	0.180	0.155	0.150	.....	.....
A. L.	0.130	0.200	.....	0.184	0.158	0.150	0.140	0.131	.....
B. A.	0.115	.....	0.206	0.200	0.152	0.140	0.130	0.120	.....
R. J.	0.105	.....	0.192	.....	0.158	.....	0.116	0.110	.....
G. S.	0.137	0.190	0.230	0.202	0.215	0.202	.....	0.147	.....
V. G.	0.110	0.240	0.186	0.185	0.150	0.130	0.120	0.110	.....
M. G.	0.127	0.176	0.160	.....	0.280	0.200	0.146	.....	.....

TABLE 3.—Blood Sugar Tests in Functional Cardiac Disorders

Case	Fasting Level, per Cent.	After Sugar Ingestion							
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.
S. D.	0.140	0.200	0.130	0.140	0.132	0.140	.....	.....	.....
S. F.	0.144	0.192	0.180	0.170	0.170	0.162	0.148	0.142	.....
T. V.	0.140	0.150	.....	0.156	0.148	0.115	0.130	.....	.....
B. F.	0.130	0.170	0.190	0.165	0.142	0.132	0.130	.....	.....
J. J.	0.100	.....	0.164	.....	0.160	0.140	0.130	0.120	.....
L. E.	0.119	0.119	0.140	0.173	0.125	0.102	0.110	.....	.....
S. C.	0.095	0.125	0.081	0.093	0.100	0.100	.....	.....	.....
N. H.	0.110	.....	0.130	0.119	0.110	0.100	.....	.....	.....
R. R.	0.083	0.074	0.070	0.092	0.074	0.090	.....	.....	.....
E. W.	0.105	0.190	0.166	0.130	0.090	0.095	.....	.....	.....

The fairly high fasting level, or hyperglycemia; the high peak and the delayed assimilation curve in each of the nine cases classified as mild hyperthyroidism (Table 2), shows the similarity which exists, from a laboratory standpoint, between this group and the exophthalmic goiter patients. Two of the six patients whose urine was examined during the test showed glycosuria or decreased tolerance.

The group reviewed in Table 3 represents those patients classified clinically as functional cardiac disorder. Two of the ten patients showed a delayed assimilation of sugar; however, the remaining tests performed on the entire group gave normal figures. The fasting blood sugar level was slightly higher than normal in four of the patients, though the same fasting level was found in normal controls. The long walk from the ward to the laboratory just prior to the blood withdrawal may have been a factor. The normal controls were laboratory technicians actively engaged at work, the hour preceding the test. Note, therefore, the much lower fasting level, the lower peak, and the more rapid assimilation in this cardiac group compared with the previous tables. The sugar tolerance was not decreased in any of the five patients examined for glycosuria.

TABIE 4.—Blood Sugar Tests in Miscellaneous Disorders

Case	Diagnosis	Fasting Level, per Cent.	After Sugar Ingestion								Glycosuria, Hourly Tests
			½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.	
F. J.	Hypopituitarism	0.080	.....	0.188	0.180	.....	0.120	.....	0.115	0.096	None
M. A.	Simple goiter	0.100	.....	0.118	0.200	0.188	.....	0.102	.....	.....	None
L. L.	Simple goiter	0.100	0.085	0.200	0.100	0.100	.....	.....	.....	.....	None
P. B.	Hysteria	0.105	0.108	0.107	0.121	0.094	0.089	.....	.....	.....	.....
K. N.	Moron	0.105	0.180	0.120	0.118	0.111	0.098	0.092	.....	.....	.....
C. F.	Endarteritis obliterans	0.064	0.100	0.102	0.088	0.076	0.082	.....	.....	.....	.....

TABLE 5.—Blood Sugar Tests in Healthy Normal Controls

Case	Fasting Level, per Cent.	After Sugar Ingestion				Sugar Tolerance
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	
H. W.	0.120	0.168	0.150	.....	0.120	Normal
M. D.	0.118	0.159	0.140	0.120	0.115	Normal
S. L.	0.140	0.175	0.142	0.130	.....	Normal
A. Y.	0.137	0.171	0.165	0.128	.....	Normal

In the two patients diagnosed clinically as simple goiter (Table 4), note the normal sugar curves: no hyperglycemia and normal assimilation time. The patient whose case was diagnosed clinically as hypopituitarism, showed a low fasting level, a delayed assimilation and normal tolerance. The patient with endarteritis showed hypoglycemia, a very low peak and slight delay in assimilation.

In Table 5 note the two fasting levels higher than normal. As already mentioned, the fact that the controls were laboratory technicians actively engaged a whole hour previous to the test probably accounts for the higher figures. My own fasting level is 0.095 per cent.

The group analyzed in Table 6 represents six patients discharged or transferred from the hospital with a clinical diagnosis of exoph-

thalmic goiter. All of the patients' blood showed hypoglycemia, sugar curves with low peaks and normal assimilation time. On the results of this test, hypofunction of the thyroid is suggested, but, of course, a diagnosis could not be advanced. Hypothyroidism may be present in exophthalmic goiter. Reference to this fact will be referred to in the discussion.

RESULTS OF THE EPINEPHRIN SENSITIVE TEST

According to Goetsch, "in states of hyperthyroidism, there is a hypersensitiveness to adrenalin, . . . administered hypodermically . . . which hypersensitiveness is proportional . . . to the degree of hyperthyroidism present . . . In a so-called positive reaction, . . . a subcutaneous dose of adrenalin is characterized by an early rise in blood pressure, and pulse, varying from 10 to 50 and normally proportional to the degree of toxicity present. . . . There is also moderate exaggeration of the symptoms, such as asthenia, tremor, throbbing, vasomotor changes, apprehension and nervousness."

TABLE 6.—BLOOD SUGAR TESTS ON CASES DIAGNOSED EXOPHTHALMIC GOITER, WITH PROBABLE HYPOFUNCTION

Case	Fasting Level, per Cent.	After Sugar Ingestion				
		½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.
Z. W.	0.072	....	0.095	0.065	0.050	0.073
D. G.	0.070	0.083	0.095	0.073	0.067	0.075
C. R.	0.070	0.050	0.055	0.105	0.060	0.064
A. S.	0.063	0.116	0.087	0.081	0.070	0.060
M. A.	0.055	0.055	0.052	0.075	0.075	0.045
B. J.	0.077	0.080	0.084	0.082	0.085	0.077

The record of a positive epinephrin test on one of the patients is shown in Table 7.

The results recorded in Table 8 do not appear to establish the Goetsch epinephrin sensitive test as infallible in the diagnosis of hyperfunctional activity of the thyroid gland. It proved negative in a case of frankly toxic exophthalmic goiter and positive in two cases of functional cardiac disorder. A positive reaction seems more likely to be a measure of the sensitization of the sympathetic or vegetative nervous system, whatever the exciting cause, rather than a hyperfunction of the thyroid gland. The presence or absence of glycosuria, within two hours following the injection of 0.5 c.c. of a 1:1,000 epinephrin solution, when studied in conjunction with the pulse and blood pressure, is a factor to be considered in a diagnosis based on this test. Two of the above five cases with positive epinephrin tests on the thyroid group had an associated glycosuria. There was no glycosuria with the two positive epinephrin tests in functional cardiac disorder.

TABLE 7.—Results of Epinephrin Tests on Private J. R. R., Company A, 340th Infantry, Nov. 1, 1918. Diagnosis, Early Hyperthyroidism

Nov. 1, 1918 p. m.	Pulse	Respiration	Blood Pressure S. D.	Symptoms	
				Subjective	Objective
3:35	92	20	140-80	Comfortable; mentally quiet; no fear; no pain; no palpitation; mouth moist	Jugular pulsation and throbbing in neck fairly pronounced. Hands cool, moist. Face slightly flushed; no cyanosis
3:45	91	20	140-76		
3:50	Urine collected for sugar test			(Urine negative for sugar)	
4:00	Epinephrin, 7½ min., 1:1,000 subcutaneously				
4:05	110	18	150-66	Throbbing in epigastrium and arm. Pain in left arm	Throbbing more prominent in vessels of neck. Throbbing in epigastrium
4:15	112	18	170-60	Throbbing or pumping not so evident. Thrill felt over entire body	Throbbing more prominent in neck and epigastrium. Pupils dilated. Slight cyanosis of hands. Feet cool
4:20	112	22	140-60	Thrill still felt through body. Mouth feels moderately dry	As before. Hands cool and moist. Throbbing still prominent
4:25	116	20	161-50	Not uncomfortable	Throbbing about same. Pupils still dilated
4:30	116	20	160-50	Slight pain on breathing, precordidal. Feels warm in face	Slight epigastric pulsation. Feet cold. Hands cool
4:35	120	22	146-52	About the same	As above
4:40	120	18	150-80	Pain in left arm radiating from site of hypodermic injection	Skin of arm at site of injection white, blanched. Hands cool, moist
4:40	Urine collected for sugar test			(Urine positive for sugar)	
4:45	112	22	150-80	Feels about same	As above. Pupils still dilated
4:50	120	16	150-80	No change	Pulsation in arm and epigastrium much diminished
4:55	116	20	150-80	Throat feels dry. Otherwise feels about normal. Arm feels sore at injection site	Pulsation in neck as before test. Pupils still dilated
5:00	108	16	142-80	About same	Epigastric pulsation hardly perceptible. Otherwise as above
5:30	Urine collected for sugar test			(Urine, trace of sugar)	

Interpretation: Test reveals a moderate hypersensitiveness to epinephrin, with a moderate exaggeration of symptoms, with slight glycosuria.

TABLE 8.—The Epinephrin Test in Cases of Thyroid and Functional Cardiac Disorders

Case	Diagnosis	Result	Glycosuria
A. L.	Mild hyperthyroidism	Positive	
L. C.	Mild hyperthyroidism	Negative	
R. J.	Mild hyperthyroidism	Positive	Trace
V. H.	Mild hyperthyroidism	Positive	None
R. H.	Exophthalmic goiter	Positive	
R. B.	Exophthalmic goiter	Negative	
D. G.	Exophthalmic goiter	Positive	Trace
B. E.	Exophthalmic goiter	Positive	
B. F.	Functional cardiac disorder	Negative	None
F. M.	Functional cardiac disorder	Positive	None
F. C.	Functional cardiac disorder	Positive	None
L. F.	Functional cardiac disorder	Negative	None

III. RESULTS OF TESTS FOR NITROGEN LOSS

It has long been established that nitrogen metabolism, in exophthalmic goiter, is increased. There is a nitrogen loss by way of the kidneys and the bowel. Total nitrogen and ammonia nitrogen of the urine were therefore recorded. In line with recent investigations and from a considerable amount of evidence accumulated by Benedict and by Cathcart in 1907 and later by Orr,[4] to show that privation of carbohydrates, or any derangement of its metabolism leads to an excretion of creatin in the urine, creatinin and creatin were therefore estimated.

On account of lack of facilities in weighing diets and measuring the nitrogen intake, the results of nitrogen elimination in the urine is therefore only suggestive. The creatin figures I consider to be more conclusive. All patients were ambulatory, all had the same so-called ward diet: meat once a day, vegetables, bread, butter, milk, coffee, puddings, fruit and occasionally eggs. The urine was collected under exact and proper supervision and preservation.

TABLE 9.—PROTEIN METABOLISM IN THYROID AND FUNCTIONAL CARDIAC DISORDERS

Case	Diagnosis	Urine			
		Total N, Gm.	Ammonia, C.c.	Creatinin, Gm.	Creatin, Mg.
H. T.	Exophthalmic goiter	7.29	309	1.0	50
R. B.	Exophthalmic goiter	15.80	1,103	1.58	170
B. E.	Exophthalmic goiter	10.65	641	2.32	110
L. C.	Mild hyperthyroidism	7.30	...	1.25	80
A. L.	Mild hyperthyroidism	14.95	584	1.97	30
B. A.	Mild hyperthyroidism	11.70	890	1.46	210
R. J.	Mild hyperthyroidism	14.92	708	1.82	430
S. D.	Functional cardiac disorders	12.00	...	1.21	10
S. F.	Functional cardiac disorders	4.59	402	0.69	3
T. V.	Functional cardiac disorders	11.18	...	1.45	0
B. F.	Functional cardiac disorders	6.94	442	2.10	27

The methods of Folin were employed in the estimation of total nitrogen, creatinin and creatin. The ammonia is expressed in terms of tenth normal acid. The chapter on quantitative analytical methods in Medical War Manual No. 6, U. S. Army, proved a reference handbook of value throughout the investigations.

In Table 9 note the very low (normal) figures for creatin in the four cases of functional cardiac disorder. The four cases of mild hyperthyroidism show an increased creatin output in twenty-four hours. A similar increase in creatin was found in the three goiter cases recorded. The creatinin output did not show a corresponding increase, remaining within normal limits in the three groups examined. For total nitrogen the figures for high output through the kidneys are found in the thyroid groups. The ammonia nitrogen

4. Orr: Biochem. J., October, 1918.

figures for the thyroid groups are also higher than normal. One exophthalmic goiter patient (H. T.) with a comparatively low nitrogen output, also had a rather low blood sugar fasting level, which leads to the assumption that metabolic changes in this patient were at the time not increased. The goiter was of several years duration. Thus, the total nitrogen, creatin and ammonia output in the urine showed higher figures in the thyroid cases.

IV. TESTS FOR ACIDOSIS, THE RESULT OF A TOXIC FUNCTIONAL ACTIVITY OF THE THYROID GLAND

The severer symptoms and the more striking stigmata of acute toxic goiter are suggestive of an acid intoxication, with depletion of the blood carbonates; similar in fact to the symptoms observed in the oxybutyric acidosis of diabetes and of the food intoxications in children. The symptoms of toxemia include extreme restlessness. tachycardia, vasomotor changes, tremors, dyspnea, loss of weight and psychic disturbances. Kuriyama[5] produced acidosis in rabbits by thyroid feeding, but had negative results after injections of epinephrin.

Methods.—The measure of acidosis was estimated indirectly by Sellards'[6] sodium bicarbonate tolerance test, Folin's, and also Henderson's[7] tests for titratable and total acidity, and by Marriott's[8] test for the alveolar air CO_2 tension.

The sodium bicarbonate tolerance test proved the more applicable to the three groups studied, and revealed a lessened alkalinity of the blood in the thyroid patients. This test should be performed not less than three hours after a meal, as food for an average diet has a tendency to render urine, passed just following a meal, alkaline. According to Sellards,[6] 10 gm. is the average upper level of alkali required for ingestion, in order that the urine may become neutral or alkaline.

Marriott's alveolar air CO_2 test for acidosis was also applied, but results even in the functional cardiac disorders were often found below the normal from 40 to 45 mm. CO_2 tension. It is generally accepted that a decreased CO_2 tension of alveolar air, when found associated with cardiac disorders, is primarily a result of pulmonary-circulatory disturbances. It is not, therefore, the method of choice when applied to cardiac or pulmonary diseases.

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5. Kuriyama, S.: The Influence of Thyroid Feeding on Carbohydrate Feeding. J. Biol. Chem. **33**:215 (Jan.) 1918.

6. Sellards, A. W.: Acidosis, 1917.

7. Henderson, L. J.: Total Acidity of Urine, J. Biol. Chem., 1911, No. 9, p. 403; also see War Manual No. 6.

8. Marriott, W. McK.: A Method for the Determination of the Alveolar Carbon Dioxid Tension, J. A. M. A. **66**:1594 (May 20) 1916.

The free (titratable) acidity and the total acidity (the phenol-sulphonephthalein, formaldehyd titration method) are expressed in terms of tenth normal acid: 600 c.c. is high normal for titratable acidity; 1,600 c.c. represents the maximum normal figure for total acidity of the urine.

TABLE 10.—EXAMINATION OF PLASMA CO_2, ALVEOLAR AIR CO_2 TENSION AND URINE

Case	Diagnosis	Plasma CO_2 Volume, per Cent.	Alveolar Air CO_2 Tension, Mm.	Urine		
				Sodium Bicarbonate Tolerance, Gm.	Titratable Acidity, C.c.	Total Acidity, C.c.
H. T.	Exophthalmic goiter	52	34.0	Over 20	...	1,695
B. E.	Exophthalmic goiter	..	28.3	15	516	1,157
D. G.	Exophthalmic goiter	..	30.0	10	945	.....
L. C.	Mild hyperthyroidism	..	31.3	15	674	.....
A. L.	Mild hyperthyroidism	..	33.0	15	613	1,197
B. A.	Mild hyperthyroidism	..	31.7	10	1,100	1,990
R. J.	Mild hyperthyroidism	..	31.0	20	592	1,300
M. A.	Mild hyperthyroidism	..	34.0	15	642	.....
S. D.	Functional cardiac disorder	..	36.0	Alkaline	363	.....
S. F.	Functional cardiac disorder	..	32.0	5	521	983
T. Y.	Functional cardiac disorder	..	36.0	10	720	.....
B. F.	Functional cardiac disorder	..	31.3	10	294	736
J. J.	Functional cardiac disorder	..	40.0	10	...	1,510
F. J.	Functional cardiac disorder	..	32.0	5	313	.....

In one exophthalmic goiter patient (Table 10) with apparently a severe toxemia, the plasma CO_2 is recorded as fifty-two volumes per cent. This figure is the upper level of acidosis, and therefore mild in degree. Normal limits of blood plasma CO_2 are from 65 to 75 volumes per cent. Note in the thyroid groups the higher amounts of sodium bicarbonate required to make the urine neutral or alkaline. Tests for titratable and total acidity of the urine give also increased results in the thyroid patients.

CASE 2.—PRIVATE E. B., SEVENTH BATTALION, 153 D. B.

Weight, 147½ pounds; height, 70½ inches; livestock buyer; 24 years of age; married; in service three months. Diagnosis, August 6, heat exhaustion. L. O. D. August 13, exophthalmic goiter. E. P. T. E. August 13, chalazion (left lower lid), E. P. T. E.

Sugar Tolerance Test	Urine	Coagulation Time	Alveolar CO_2 Tension
Blood. 8/15/18 150 pounds weight 1.75 gm. per kilogram; 120 gm. sucrose a.m. 8:00-1-127 mg. per 100 c.c. before sucrose 8:30-2-134 mg. per 100 c.c. after sucrose 9:00-3-162 mg. per 100 c.c. after sucrose 9:30-4-200 mg. per 100 c.c. after sucrose 10:00-5-164 mg. per 100 c.c. after sucrose 10:30-6-166 mg. per 100 c.c. after sucrose 11:00-7-145 mg. per 100 c.c. after sucrose 11:30-8-135 mg. per 100 c.c. after sucrose 12:00-9-135 mg. per 100 c.c. after sucrose Poor assimilation for sugar	1.75 gm. per kilogram; 120 gm. sucrose 8:00 before sucrose—negative Benedict 9:00 after sucrose—negative Benedict 10:00 after sucrose.. negative Benedict 11:30 after sucrose—negative Benedict	4½ minutes	8/16 28.3 mm. tension Normal 35 to 45 mm.

Indican	Titrable Acidity (Urine)	Sodium Bicarbonate Tolerance Test, Urine	Blood Examination	Goetsch Epinephrin Test
9/14 Negative	8/21 Sp. Gr. 1.016 8/28 Amount 516 c.c. N/10 acid (Normal) 9/14 Total acidity, 1,157.7 c.c. N/10	8/27 3.15 urine acid 3.20 5 gm. sodium bicarbonate 3.45 urine acid 3.50 5 gm. sodium bicarbonate 4.15 urine acid 4.20 5 gm. sodium bicarbonate 4.45 urine alkaline	Lymphocytes 29% Large mononuclears.... 8% Total..... 37% Normal	8/23 Moderate reaction

Fluoroscopic Examination: Sept. 5, 1918. Thyroid: showed bilateral enlargement (moderate) of thyroid gland. Thymus: no shadow.
Reaction to Typhoid Inoculation: Moderately severe.
Urine: 24 hours.—Total nitrogen, 10.65 gm.; creatinin, 2.32 gm.; creatin, 0.105 gm.
This is a complete record of clinical and laboratory tests such as were made on many of the patients studied.

DISCUSSION

In MacCurdy's book, "War Neuroses," [9] the general conclusion is expressed that most of the cases in soldiers of "disordered action of the heart" are not neurotic in the narrow sense, but are to be regarded as of organic origin, either from some endocrine disorder, disturbance of the vegetative nervous system, or involvement of the inherent cardiac mechanism. However, as pointed out above, it is agreed with Addis and Kerr[10] that enlargement of the thyroid in some patients with a cardiac neurosis may be incidental and not causative.

The above studies represent an effort to detect early hyperthyroidism in patients classified among the heart neuroses cases. I believe that four or five patients, by means of laboratory tests, did show hyperfunctional activity of the thyroid.

The presence of disordered thyroid function has been previously recognized and reported by medical officers since the outbreak of the great war. Beebe[11] asserts that many cases of "soldier's heart," are in reality cases of hyperthyroidism. Brooks[12] reported a large number of hyperthyroid disorder developing among soldiers at Camp Upton. Ewing[13] points out that a persistent thymus may often be the underlying factor responsible for the "irritable heart" and "irritable thyroid" of soldiers. Other writers give the impression that thyroid enlargement is almost constantly associated with the functional cardiac disorder syndrome. It has been a new experience to find disturbance of the thyroid so prevalent in young men. Should appropriate metabolic tests have been performed upon this seemingly large thyroid disorder group, the great majority would have proved simple physiological enlargement, nontoxic and compensatory, following upon overstrain.

9. MacCurdy, J. T.: War Neuroses, New York, G. P. Putnam's Sons, 1918.
10. Addis, Thomas, and Kerr, W. J.: Relative Frequency in Recruits with and without Thyroid Enlargement, etc., Arch. Int. Med. **23**:316 (March) 1919.
11. Beebe, S. P.: Med. Rec. **93**:337 (Feb. 9) 1918.
12. Brooks, Harlow: Am. J. M. Sc. **156**:726 (Nov.) 1918.
13. Ewing, J.: J. A. M. A. **71**:1525 (Nov. 9) 1918.

It is impossible, therefore, to entirely concur with the numerous investigators who have based a diagnosis of hyperthyroidism on symptoms and signs of vasomotor or nervous instability, symptoms and signs that other workers have unreservedly ascribed to a heart neurosis, calling the syndrome "neurocirculatory asthenia, irritable heart, effort syndrome, constitutional inferiority or cardiac defect functional."

One great fact that has clarified our understanding of thyroid derangement, is the recognition that exophthalmic goiter does not mean hyperthyroidism; that even toxic exophthalmic goiter symptoms frequently occur with hypothyroidism, in 23 per cent. of cases, according to Bertine.[14] Thyroid deficiency is present not only in myxedema, but at puberty, during pregnancy and following overstrain.

Therefore, hypertrophied thyroid, or goiter, does not mean hyperfunction. Hyperthyroidism is a misnomer, and a new word is needed to express the metabolic derangement caused by hyperfunctional activity of the thyroid.

An increase in basal metabolism, a nitrogen loss and hyperglycemia are recognized laboratory findings in hyperthyroidism. Creatinuria is present in exophthalmic goiter and in hyperthyroidism.[15] The following outline is my understanding of the present accepted theory of hyperthyroidism and hypothyroidism.

Disorder	Pathology	Type	Effect	Associated
Hyperthyroidism	Excess of normal hormone	Enlarged	May be toxic	May have exophthalmus
Hyperthyroidism	Excess of unsynthetized hormone	May be small	May be toxic	May have exophthalmus
Hypothyroidism	Deficiency of normal hormone	May be large	Nontoxic	No exophthalmus
Hypothyroidism	Small amount abnormal hormone	Enlarged or small	Toxic	May have exophthalmus

Creatinuria.—Though creatinin is a normal, and for each individual a fairly constant constituent of the urine, creatinuria, with few exceptions, is the result of a disturbance of metabolism. I agree with Mendel and Rose,[16] Orr and others, that the output of creatin is inversely proportional to the amount of carbohydrates ingested. It is increased also in starvation. Creatin is mostly endogenous, namely, from the tissues, but its loss in the urine depends on a derangement in carbohydrate, rather than in protein metabolism.

The intimate correlation and interaction of the glands of internal secretion, actively assisting in the direct control of the body metab-

14. Bertine, E.: Med. Rec. **90**:895 (Nov. 18) 1916.
15. Denis, W.: J. Biol. Chem. **30**:47 (May) 1917; **30**:189 (June) 1917; **31**:561 (Sept.) 1917.
16. Mendel, L. B., and Rose, W. C.: J. Biol. Chem. **10**:213, 1912.

olism in growth and repair, makes difficult the localization of functional disorders in the endocrine gland system. The recognized fact that the etiology of heart neuroses is still a big problem, and that the early diagnosis of hyperthyroidism by symptoms alone is almost an impossibility, should prompt the clinician or surgeon familiar with the newer laboratory and clinical tests to study his functional cardiac and endocrine disorder patients with the aid of these analytical methods.

SUMMARY

1. The laboratory affords the most reliable means toward the recognition of early hyperthyroidism.

2. Early hyperthyroidism may be the cause of a heart neurosis. Simple, physiologic, goiter may be found associated with functional disorder of the heart, without evidence of hyperthyroidism.

3. The sugar tolerance test seems an important aid in the detection of borderline cases or early hyperthyroidism.

4. The epinephrin test did not prove, in the study of the cardiac neuroses, diagnostic of hyperthyroidism. It seemed rather an index of the sensitization of the sympathetic nervous system. Its value as a diagnostic test is increased when blood and urinary sugar estimations are recorded with pulse rate and blood pressure. Intramuscular injections gave best results.

5. Tests for nitrogen loss and acidosis seemed suggestive as aids in the diagnosis of toxic hyperthyroidism. Further studies are being made to discover if borderline cases or early hyperthyroidism reveal such changes. Creatinuria did seem present in the thyroid disorder group, and when taken in conjunction with the other tests, was of value in the diagnosis of early hyperthyroidism.

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THE CONTROL OF ACIDOSIS IN THE TREATMENT OF DIABETES *

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INTRODUCTION

During the past five years marked advances have been made in the treatment of diabetes, due largely to the introduction by Allen of the "fasting method." In the practical application of this method of treatment the patient is fasted until glycosuria disappears; and subsequent to the initial fast, fasting is employed to such an extent as is necessary to aid in keeping the patient free from glycosuria. In other words, the most important and significant sign or symptom by which the therapeutic regime is regulated is the presence or absence of sugar in the urine. Allen, however, has emphasized the fact that in diabetes a disturbance of the entire metabolic mechanism of the body is present, and that the presence or absence of glycosuria at any given time is but a crude test of the state of that function, though practically it is the best test available. In the latest publication,[1] stress is laid on the importance of the state of the blood sugar, and attention is also drawn to the importance of acidosis.

The questions of the nature of acidosis and the relationship between changes in alkaline reserve and clinical symptoms have been discussed in previous papers from this Hospital (Van Slyke and Cullen;[2] Stillman, Van Slyke, Cullen and Fitz;[3] Fitz,[4] 1917; Palmer and Van Slyke[5]). Suffice it to say that although other factors, including, perhaps, unknown toxins, can also cause diabetic collapse (Fitz[4]), as a rule, the severity of the clinical symptoms parallels the fall in plasma bicarbonate; moreover, the plasma bicarbonate begins to fall before the symptoms appear.

The introduction of more exact methods for the study of acidosis, in particular, methods for determining blood plasma bicarbonate, and the opportunity for combined clinical and laboratory studies on a group

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* From the Hospital of the Rockefeller Institute for Medical Research, New York.

1. Allen, F. M., Stillman, E., and Fitz, R.: New York, Monograph of the Rockefeller Institute, 1919, No. 11.
2. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:289, 347, 389, 401, 405 (June) 1917.
3. Stillman, E., Van Slyke, D. D., Cullen, G. E., and Fitz, R.: J. Biol. Chem. **30**:405 (June) 1917.
4. Fitz, R.: Proc. Assn. Am. Phys. **32**:155, 1917; **30**:389, 405 (June) 1917.
5. Palmer, W. W., and Van Slyke, D. D.: J. Biol. Chem. **32**:499 (Dec.) 1917.

of patients, selected chiefly for the severity of their diabetes, have resulted in the gradual development in this clinic of systematic procedures, first, for ascertaining the individual reactions of the patient in regard not only to his carbohydrate tolerance, but also his tendency toward acidosis, and second, for guiding the treatment by the metabolic reactions that have been ascertained. The present paper is an outline of these procedures.

LABORATORY CONTROL

The minimum laboratory control with which satisfactory results may be considered possible consists of qualitative glucose and acetoacetic acid tests on the daily urine samples, with determinations of plasma bicarbonate when the urine shows a strong test for acetoacetic acid, or when any of the clinical signs are unfavorable. The symptoms of incipient acidosis are extremely variable; they may include indefinite malaise, headache, slight nausea, neuralgic pains, or almost any abnormal symptom. Consequently, the slightest unfavorable clinical sign at any stage of treatment should be taken as an indication for determining the plasma bicarbonate.

It is desirable, also, especially for patients whose condition is uncertain or who are being put on a new regimen, to determine quantitatively the blood sugar and the daily excretion of sugar and acetone bodies in order to follow the progressive effect of the treatment. We have usually determined the blood sugar whenever blood was drawn for bicarbonate estimation.[6]

OUTLINE OF ROUTINE

For the most expeditious creation and maintenance of an aglycosuric and aketogenic state, the routine evolved in applying the prin-

6. The methods used in this clinic have been the following: Blood plasma bicarbonate: CO_2 capacity method, Van Slyke and Cullen[7] (the titration method of Van Slyke, Stillman and Cullen[7] was not available at the time these observations were made). Blood sugar: Lewis and Benedict method, as modified by Myers and Bailey.[8] Urinary sugar: qualitative, Benedict;[9] quantitative, Benedict (1911). Acetone bodies in urine: qualitative, the well known ferric chlorid test of Gerhardt, described in all laboratory manuals; quantitative, Van Slyke.[10] Acetone bodies in blood: quantitative, Van Slyke and Fitz.[11] Titrable acids in urine: Folin.[12] Ammonia in urine: Van Slyke and Cullen.[13]

7. Van Slyke, D. D., Stillman, E., and Cullen, G. E.: J. Biol. Chem. **38**: 167 (May) 1919.

8. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:147 (Feb.) 1916.

9. Benedict, S. R.: J. Biol. Chem. **5**:485, 1908; **9**:57, 1911.

10. Van Slyke, D. D.: J. Biol. Chem. **32**:455 (Dec.) 1917.

11. Van Slyke, D. D., and Fitz, R.: J. Biol. Chem. **32**:495 (Dec.) 1917; **37**:551 (April) 1919.

12. Folin, O.: Am. J. Physiol. **9**:265, 1903.

13. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **19**:211, 1914; **24**:117 (Feb.) 1916.

ciples of the fasting treatment in this hospital may be outlined as follows:

1. A preliminary observation diet.
2. The creation of the aglycosuric and aketogenic state by either continuous or intermittent fast.
3. Estimation of the individual carbohydrate tolerance.
4. Determination of the maintenance diet.
5. Final observation period.

The significance, according to our experience, of acidosis in each stage of the treatment and its consideration in modifying the treatment are indicated in the following pages.

1. *The Preliminary Observation Diet.*—On admission to the hospital patients not suffering from acidosis have been placed on the following observation diet in order to ascertain their behavior under standardized conditions (See Table 4).

TABLE 1.—OBSERVATION DIET

Protein, Gm.	Carbohydrate, Gm.*	Fat, Gm.
1.5 per kilogram	10 - 25	Sufficient to bring total calories to 35 per kilogram body weight

* Carbohydrate in the form of green vegetables only, from 10 to 25 gm. according to apparent severity of the case.

Acidosis of the moderately severe or severe type (plasma bicarbonate CO_2 below 40 volumes per cent.) has been considered the one contraindication to placing the patient on the observation diet and maintaining him on it for the usual length of time. Such patients have been put on fasting directly on admission to the hospital as requiring immediate and active treatment (Table 5).

2. *Creation of the Aglycosuric State by Continuous or Intermittent Fast.*—After the period of the observation diet, the patient is placed on a continuous fast (Tables 4, 5 and 6). This is continued until the patient is rendered aglycosuric unless acidosis develops. By the continuous fast is meant absolute abstinence from all foods containing any demonstrable amount of carbohydrate, protein or fat, continued without interruption until the patient has been made sugar free for twenty-four hours. In our series of cases this has required from two to eleven days. Fluids, in the form of clear soup, coffee and water, are taken daily in a total amount of at least from 1,500 to 2,000 c.c.

In occasional instances (one out of sixteen in our cases which were, of course, selected for their severity) continuous fasting has resulted in the development of dangerous acidosis. Consequently, patients on continuous fasts have been watched carefully for this development. The clinical symptoms of incipient acidosis have been found to vary so extremely that any local or general malaise has come to be looked on with suspicion. The only reliable tests have been found to be those of the laboratory. It seems well to emphasize here that we have come

to believe that during the fasts accurate daily determinations of the plasma bicarbonate should be performed to obviate a certain percentage of fatalities.

In the cases developing or retaining acidosis on the continuous fast (Table 7), as shown by plasma bicarbonate much below normal, continuous fast has been changed to the intermittent fast. Its object is the same as that of the continuous fast—namely, the creation of an aglycosuric state—and its substitution has been made solely when acidosis has resulted from the more expeditious continuous method.

By the intermittent fast is meant an absolute fast, for periods of time depending on the reaction of the patient, from all foods containing any demonstrable amount of carbohydrate, protein, or fat, the fasting periods being interrupted by intervals of diets low in caloric value (see Table 7 and accompanying description).

The manner in which the continuous and intermittent fasting treatments have been applied has been governed by the state and behavior of the bicarbonate reserve of the patient's blood.

(a) In cases with no acidosis or only mild acidosis, as determined before the institution of fasting, a moderate fall in the plasma bicarbonate has been permitted before the continuous fast was abandoned for the intermittent.

(b) If the existing acidosis was moderately severe (plasma bicarbonate CO_2 of from 30 to 40 volume per cent.) even a drop of two or three volume per cent. in bicarbonate, especially if the fall was progressive, was sufficient to cause interruption of the fast.

(c) In cases in which the bicarbonate determination showed a severe acidosis (plasma bicarbonate CO_2 below 30 volume per cent.) active treatment was instituted as follows:

Sodium bicarbonate: 3 gm. per hour, dissolved in cold water, until the bicarbonate of the blood became normal.

Fluids: Forced to the limit, but not to the extent to cause nausea; it has been attempted to give about 5,000 c.c. of fluid during the twenty-four hours.

Coffee: Clear, very strong coffee has been given to stimulate the renal action of patients suffering from severe acidosis. As much as from 1,200 to 1,500 c.c. of coffee has been given during the day.

Whisky: No beneficial effect on the acidosis has been obtained from giving alcohol, and it has apparently nauseated in some instances; therefore, the use of whisky as a therapeutic measure for acidosis has been discontinued in this hospital.

Catharsis: Active catharsis by calomel and salts, together with high colon irrigations until the washings are returned without fecal matter, has been instituted. We have no exact data as to the part which this

treatment has had in ameliorating the acidosis, but clinically the effects have seemed to be beneficial.

Diet: Continuous fasting has been applied directly on admission. If from six to twelve hours' fasting, together with the above treatment, did not cause an increase in the plasma bicarbonate, light feeding was begun. It was thought theoretically correct that such feeding should be principally protein, as carbohydrate in such cases is not burnt, and could only add to the severity of the diabetes, while fat leads to the formation of ketone bodies and consequent direct increase in acidosis. Therefore, from 600 to 800 calories have been given in the form of eggs and lean meat (see Table 7).

In the treatment of acidosis we have found that nausea is the condition above all others to be avoided, because if it becames uncontrollable, successful treatment of the acidosis becomes nearly impossible. Nausea may be produced by any one of the above mentioned measures — bicarbonate therapy, the forcing of fluids, catharsis, the institution of fasting, or the institution of feeding. Experience has taught us that close clinical observation and frequent laboratory tests can, in the great majority of cases, prevent the development of nausea, if at the first sign of any intensification of it the offending factor in the treatment, whether it be forced fluids, bicarbonate, fasting or feeding, be discontinued until the symptoms of nausea disappear.

The statements bearing on the degree of acidosis and the laboratory indications for changing from continuous to intermittent fasting are summarized in Table 2.

TABLE 2.—DEGREE OF ACIDOSIS AND LABORATORY INDICATIONS FOR CHANGING FROM CONTINUOUS TO INTERMITTENT FASTING

Degree of Acidosis	CO_2 Combining with 100 C.c. of Blood Plasma, C.c.	Acid Excretion* $\frac{N/10\ NH_3 + Acid}{Kg.\ Body\ Weight}$ C.c.	Drop of CO_2 Permitted before Interrupting Fast, C.c.
No acidosis	Over 50	0 to 27	To 45
Mild acidosis	50 to 40	27 to 65	Drop of 10 to 5
Moderately severe acidosis	40 to 30	27 to 100	Drop of 8 to 2
Severe acidosis	Below 30	Over 100	Fast interrupted after 6 to 12 hours unless CO_2 rises with treatment outlined above

* Concerning the interpretation of the relationship of the urinary acid excretion figure, $\frac{N/10\ NH_3 + titratable\ acid}{Kg.\ body\ weight}$, to severity of acidosis, the reader is referred to the discussion in paper X of the Studies of Acidosis (Van Slyke, 1918). The ordinary correspondence between these figures and the degree of acidosis is indicated by the table.

Estimation of the Individual Carbohydrate Tolerance on a Diet of Green Vegetables Alone.—After the patient has been made aglycosuric by the fasting method and has remained aglycosuric for twenty-four hours, he has been placed on a graduated carbohydrate tolerance test. This test has been performed by giving a diet comprised of green vegetables alone, starting the test

with green vegetables containing 10 gm. of carbohydrate and increasing the amount of carbohydrate 10 gm. each day, until glycosuria results (Tables 4, 5, 6 and 7). Occasionally a trace of sugar has been found to occur in the urine during the first days of the test. This not infrequently has been found to clear up without fasting, and the patients have frequently shown an ability to metabolize many times the amount of carbohydrate that the first sugar reaction seemed to indicate was the limit of their tolerance. Therefore, on the first appearance of glycosuria we have continued the same amount of carbohydrate for another twenty-four hours; if, at the end of this time, there was cessation of the sugar excretion, the test was continued, the carbohydrate food being increased daily until glycosuria appeared on two successive days. This point we have considered as indicating the carbohydrate tolerance for the individual under observation. Fasting was then again instituted until the patient had become sugar free for twenty-four hours. The determination of the maintenance diet was then begun.

The carbohydrate tolerance test establishes a basis for comparison with later tests, whereby the progress of the patient can be determined, and also affords a basis for the initial maintenance diet as described below.

In cases in which although acidosis has been benefited by fasting, but has not been entirely eradicated, the carbohydrate test diet has usually raised the blood bicarbonate to a full normal. The ketonuria, also, which has usually accompanied subnormal blood bicarbonate, has been diminished or entirely stopped. The green vegetable diet may be considered almost a specific for mild acidosis. (Note its effect in Tables 4, 5 and 6 in raising plasma bicarbonate and abolishing the ferric chlorid reaction for acetoacetic acid in the urine.)

Determination of the Maintenance Diet.—By the maintenance diet is meant a mixed diet, which is as near a normal diet as can be tolerated without glycosuria and with fully normal plasma bicarbonate. After having made the patient aglycosuric and having determined the carbohydrate tolerance, it has been our custom to place him on a trial maintenance diet (Table 3).

TABLE 3.—The Trial Maintenance Diet

Per 24 Hours		
Carbohydrate	Protein	Fat
One tenth the amount tolerated on the carbohydrate tolerance test	1.5 gm. per kg. body weight	Sufficient to bring the total calorie value of the diet to 35 calories per kg. of body weight

If the diet was well tolerated and the patient appeared to need more, an increase was made in the constituents of the diet which appeared to be most needed. Care was taken that only one of the three constituents, either the fat, the protein, or the carbohydrate, was increased at a time and in a gradual systematic manner, so that should glycosuria or ketonuria result the offending food could be recognized and reduced.

Urinary tests for glucose and ketones have been made daily, while the plasma bicarbonate has been determined at least once a week, and as often after as the condition and symptoms of the patient rendered advisable (see p. 446).

When either glycosuria, definite ketonuria, or significant fall in plasma bicarbonate occurred on the maintenance diet, the patient has been put on the so-called minimum maintenance diet, which was made up exactly as the maintenance diet, except that the fat was cut down so that the patient received only twenty-five calories per kilogram body weight instead of thirty-five. Prolonged feeding (for from four to twelve weeks) of a diet of such low caloric content has frequently resulted in increased food tolerance, so that the patient could finally take the maintenance or even more than the maintenance diet. When it has been found that it was impossible to create such a tolerance, patients have been discharged on the lower diet.

If at the end of two weeks on the finally chosen maintenance diet, there has been no indication of glycosuria, no significant increase in the glycemia, and the plasma bicarbonate remains stable at a fully normal level, one may feel fairly secure that the patient in question is tolerant of the maintenance diet.

EXAMPLES OF RESULTS WITH DIFFERENT TYPES OF DIABETICS

Tables 4, 5, 6 and 7 exemplify the results obtained with patients belonging to the four groups previously described by the author (Stillman[14]). These groups are marked by characteristic differences in their tendencies toward acidosis which are briefly summarized as follows:

GROUP 1—46.8 PER CENT. OF OUR CASES.—No tendency to acidosis, either on fast or ordinary diet, regardless of degree of glycosuria.

Treatment: Made aglycosuric without danger by continuous fast. Can usually be made to tolerate fairly high calory diet without glycosuria or ketonuria. Easiest group to handle. Best prognosis.

GROUP 2—32.3 PER CENT. OF OUR CASES.—Received in condition of moderate or severe acidosis (plasma bicarbonate CO_2 below 40 volume per cent.), which clears up on fast.

Treatment: Made free of glycosuria and acidosis by continuous fast. A tendency toward acidosis is present, and the safely tolerated maintenance diet is usually lower than in Group 1.

GROUP 3—14.5 PER CENT. OF OUR CASES.—Tendency to slight acidosis (subnormal plasma bicarbonate) on any but most carefully chosen diet. Acidosis not increased by fasting.

Treatment: Glycosuria removed by continuous fast. Tolerated maintenance diet variable. Usually there is a tendency toward acidosis which may become acute on any improper diet.

GROUP 4—6.4 PER CENT. OF OUR CASES.—Either develop or retain severe acidosis (plasma bicarbonate CO_2 below 30 volume per cent.) when fasted to attain the aglycosuric state. This is incomparably more severe than the mild acidosis observed as a rule, when normal individuals are fasted, and may rapidly become fatal unless the fall in plasma bicarbonate is checked.

Treatment: Continuous fast must be given up for intermittent fast (described below). As in Group 2, the presence of a tendency toward acidosis

14. Stillman, E.: Am. J. M. Sc. **151**:505 (April) 1916.

TABLE 4.—Dietary Record of Case 2234, Group 1

Date, 1916	Day of Observation	Body Weight, Kg.	Diet				Dextrose		Evidence of Acidosis							NaHCO₃ by Mouth
									Urine						Blood: CO_2 Combined with 100 C.c. Plasma, C.c.	
			C. H., Gm.	Protein, Gm.	Fat, Gm.	Total Diet, Calories	Urine Gm.	Blood, per Cent.	$FeCl_3$ Reaction	N/10 NH_3 C.c.	N/10 Acid C.c.	N/10 NH_3 + N/10 Acid C.c.	N/10 NH_3 + Acid / Kg. Body Weight, C.c.			
Jan. 25	1	50.4	10	60.0	130	1,490	3.25	....	Moderate							
26	2	50.9	60	60.0	130	1,490	Trace	....	Heavy							
27	3	50.2	60	60.0	130	1,490	2.55	....	Moderate							
28	4	49.8	Fast				Trace	0.17	Moderate	255	218	473	9.5	61.0		
29	5	49.8	Fast				Negative	...	Moderate							
30	6	49.6	Fast				Negative	....	Moderate							
31	7	48.4	Fast				Negative	....	Moderate							
Feb. 1	8	47.8	10	4.0	0.3	60	Negative	....	Moderate							
2	9	48.0	20	7.5	1.0	120	Negative	0.15	Moderate	200	187	387	8.1	63.1		
3	10	48.0	30	10.5	1.9	180	Negative	0.14	Moderate							
4	11	48.2	40	14.0	2.2	240	Trace	0.11	Moderate	142	204	346	7.2	65.5		
5	12	48.4	50	17.5	2.4	300	Trace	....	Trace							
6	13	48.6	60	20.0	3.1	355	Negative	....	Negative							
7	14	48.0	70	23.0	4.6	425	Negative	0.10	Negative	54	83	137	2.85	72.3		
8	15	48.0	80	24.0	4.8	470	Negative	....	Negative							
9	16	48.2	90	31.0	5.1	545	Negative	0.12	Negative	43	67	110	2.3	73.9		
10	17	48.4	100	31.5	5.0	565	Negative	....	Negative							
11	18	48.6	110	34.5	5.5	645	Negative	0.09	Negative	43	42	85	1.75	68.8		
12	19	48.8	120	37.0	6.9	705	Negative	....	Negative							
13	20	48.2	130	39.0	7.0	755	Negative	....	Negative							
14	21	48.6	140	39.5	6.3	795	Negative	0.18	Negative	39	70	109	2.25	70.4		
15	22	48.8	150	43.5	7.0	860	Negative	....	Negative							
16	23	49.2	115	31.0	3.3	615	Negative	0.11	Negative	33	71	104	2.1	71.1		

TABLE 5.—Dietary Record of Case 2686, Case 2

Date, 1916	Day of Observation	Body Weight, Kg.	Diet				Dextrose		Evidence of Acidosis						NaHCO₃ by Mouth
									24 Hour Urine					Blood: CO_2 Combined with 100 C.c. Plasma, C.c.	
			C. H., Gm.	Protein, Gm.	Fat, Gm.	Total Diet, Calories	Urine, Gm.	Blood, per Cent.	$FeCl_3$ Reaction	N/10 NH_3 C.c.	N/10 Acid C.c.	N/10 NH_3 + N/10 Acid C.c.	N/10 NH_3 + Acid / Kg. Body Weight, C.c.		
Feb. 22	1	....		Fast*			23.0*	0.27	Heavy	*	*	*	*	12.2	45
23	2	27.8		Fast			41.0	0.38	Heavy	2,025	835	2,860	102	26.8	50
24	3	26.0		Fast			24.5	0.32	Heavy	1,508	598	2,106	81	38.3	30
25	4	25.4		Fast			21.0	0.28	Heavy	1,710	533	2,243	88	40.4	30
26	5	25.0		Fast			12.0	0.26	Heavy	1,495	286	1,781	70	46.0	20
27	6	25.2		Fast			12.0	....	Heavy	1,735	298	2,033	81	....	15
28	7	25.4		Fast			5.5	0.25	Heavy	1,772	220	1,992	78	49.6	
29	8	25.2		Fast			Trace	....	Moderate						
Mar. 1	9	25.2		Fast			Negative	0.21	Moderate	1 417	152	1,569	63	48.7	
2	10	25.0	10	3.9	0.4	60	Trace	....	Trace						
3	11	25.6	20	8.6	1.0	125	Slight	0.20	Trace	830	62	892	35	43.0	
4	12	26.6	20	8.6	1.0	125	Trace	....	Negative						
5	13	28.0	25	10.0	1.0	150	Trace	....	Trace						
6	14	30.0	25	10.0	1.0	150	Trace	0.22	Negative	798	47	845	28	55.0	
7	15	31.4	25	10.0	1.0	150	Trace	....	Negative						
8	16	31.8	30	11.5	1.3	180	Trace	0.26	Negative	550	42	592	19		
9	17	31.8	35	13.0	1.5	210	Trace	....	Negative						
10	18	31.6	8.8†	3.3	0.4	50	Trace	0.23	Negative	318	169	487	15	57.6	
11	19	30.4		Fast			Negative	....	Negative						
12	20	30.0	5	1.5	0.2	25	Negative	....	Negative						
13	21	29.8	10	3.8	0.4	60	Negative	....	Negative	365	57	422	14		
14	22	29.8	20	7.7	0.8	120	Negative	....	Negative						
15	23	29.4	20	8.6	0.9	125	Negative	0.12	Negative	244	48	292	12	53.6	
16	24	28.0	30	11.3	1.4	180	Negative	....	Negative						
17	25	28.4	40	14.5	1.8	240	Negative	....	Negative						
18	26	28.4	50	18.1	2.2	300	Negative	....	Negative						
19	27	28.6	60	21.3	2.5	355	Negative	....	Negative	*					
20	28	27.6	70	24.3	2.7	410	Negative	....	Negative						
21	29	26.4	80	27.3	3.2	470	Negative	0.15	Negative	.....	...	.....	.....	55.6	
22	30	26.0	90	29.9	4.5	530	Negative	....	Negative						
23	31	26.0	100	33.9	6.1	605	Trace	....	Negative						
24	32	25.2	100	33.9	6.1	605	Trace	....	Negative						
25	33	25.0	110	36.0	6.8	660	Trace	....	Negative						
26	34	25.0		Fast			Negative	....	Negative						
27	35	25.2	15	40.0	61.5	795	Negative	....	Negative						
28	36	25.6	15	40.0	83.4	1,000	Negative	0.10	.....	.....	...	.....	.....	52.2	

* Observation day of 11 hours. † Fast two meals.

TABLE 6.—Dietary Record of Case 2480, Group 3

Date, 1916	Day of Observation	Body Weight, Kg.	Diet				Dextrose		Evidence of Acidosis						NaHCO₃ by Mouth
									24 Hour Urine					Blood: CO_2 Combined with 100 C.c. Plasma, C.c.	
			C. H., Gm.	Protein, Gm.	Fat, Gm.	Total Diet, Calories	Urine, Gm.	Blood, per Cent.	$FeCl_3$ Reaction	N/10 NH_3 C.c.	N/10 Acid C.c.	N/10 NH_3 + N/10 Acid C.c.	N/10 NH_3 + Acid / Kg. Body Weight, C.c.		
Oct. 15	1	48.4	3.5	26.8	92.7	985	Heavy	0.42	Heavy						
16	2	47.6	5.0	100.0	166.0	2,000	Heavy	....	Heavy	602	—	—	—	44.5	
17	3	47.6	Fast				Heavy	....	Heavy	926	—	—	—		
18	4	47.9	Fast				Heavy	....	Heavy	757	—	—	—		
19	5	47.4	Fast				Heavy	....	Heavy	798	—	—	—		
20	6	45.5	Fast				Heavy	....	Moderate						
21	7	45.5	Fast				Heavy	0.38	Moderate	...	...	...	.....	53.2	
22	8	45.4	Fast				Heavy	....	Moderate						
23	9	45.4	Fast				Moderate	0.27	Moderate	...	...	...	.....	50.4	
24	10	45.2	Fast				Slight	....	Slight						
25	11	45.4	Fast				Negative	0.38	Slight	368	151	519	11	47.8	
26	12	45.3	10	3.5	0.5	60	Negative	0.32	Slight	...	...	...	.....	46.6	
27	13	46.1	20	8.0	1.0	125	Negative	0.27	Slight	298	101	399	9	47.5	
28	14	46.5	30	11.1	1.7	185	Negative	0.24	Negative	500	92	592	13	57.9	
29	15	46.9	40	15.9	2.0	250	Trace	0.40	Negative	296	82	378	8	56.5	
30	16	47.2	40	15.9	2.0	250	Negative	0.23	Negative	136	31	167	3	54.4	
31	17	47.2	50	17.8	5.8	315	Negative	....	Negative						
Nov. 1	18	47.6	60	20.0	4.6	375	Trace	0.14	Negative	...	...	...	.....	53.5	
2	19	47.8	60	20.0	4.0	365	Negative	....	Negative	210	7	217	6		
3	20	47.8	70	23.0	4.6	425	Negative	0.32	Negative	...	...	...	.....	57.1	
4	21	47.9	80	26.3	5.7	485	Trace	....	Negative						
5	22	47.6	90	27.7	6.6	545	Slight	....	Negative						
6	23	47.6	25*	10.0	1.2	155	Slight	....	Negative						
7	24	46.8	Fast				Negative	....	Negative						
8	25	47.8	5	75.0	126.8	1,505	Negative	0.17	Negative						
9	26	47.4	0	75.0	127.5	1,495	Negative	....	Negative						
10	27	47.8	0	75.0	126.0	1,480	Trace	0.28	Negative	...	...	...	.....	52.3	

* Partial fast day.

TABLE 7.—Dietary Record of Case 2414 (Third Admission) Group 4

Date, 1916	Day of Observation	Body Weight, kg.	Diet				Dextrose		Evidence of Acidosis						NaHCO₃ by Mouth
									24 Hour Urine					Blood: CO_2 Combined with 100 C.c. Plasma, C.c.	
			C. H., Gm.	Protein, Gm.	Fat, Gm.	Total Diet, Calories	Urine, Gm.	Blood, per Cent.	$FeCl_3$ Reaction	N/10 NH_3 C.c.	N/10 Acid C.c.	N/10 NH_3 + N/10 Acid C.c.	N/10 NH_3 + Acid / Kg. Body Weight, C.c.		
Feb. 19	1	44.6		Fast			20	0.26	Heavy	.....	.....	.....	...	26.4	
20	2	44.9	...	162.8	19.0	845	100	0.44	Heavy	4,160	1,330	5,490	122	24.2	30
21	3	44.8	...	94.0	22.8	600	87	0.47	Heavy	4,080	1,000	5,080	114	34.3	40
22	4	44.6	...	94.0	22.8	600	179	0.26	Heavy	3,885	955	4,840	108	36.0	20
23	5	44.6	...	94.0	22.8	600	103	0.26	Heavy	3,825	992	4,817	108	44.5	40
24	6	45.0	...	63.0	15.2	400	68	0.20	Heavy	2,830	706	3,536	89	47.2	40
25	7	46.0	...	63.0	15.2	400	59	0.25	Heavy	2,105	675	2,780	60	53.3	40
26	8	47.0	...	63.0	15.2	400	54	....	Heavy	.....	.....	.....	...	65.5	40
27	9	48.4	...	31.5	7.6	200	48	....	Heavy	1,705	148	1,853	38	....	25
28	10	49.0	...	31.5	7.6	200	29	0.27	Heavy	1,900	122	2,022	41	60.9	
29	11	49.8	...	31.5	7.6	200	36	....	Moderate						
Mar. 1	12	48.0		Fast			24	0.28	Moderate	890	60	950	20	60.2	
2	13	48.0		Fast			23	....	Slight						
3	14	47.4		Fast			10	0.27	Slight	620	60	680	14	54.0	
4	15	47.2		Fast			Trace	....	Negative						
5	16	47.2		Fast			Negative	....	Negative						
6	17	47.0	10	3.8	0.8	65	Trace	0.29	Negative	396	32	428	9	64.1	
7	18	47.2	10	3.8	0.8	65	Trace	....	Negative						
8	19	47.2	15	6.5	1.1	100	Trace	0.33	Negative	350	18	308	7	64.4	
9	20	46.2	20	7.7	0.8	120	Trace	....	Negative						
10	21	46.2	25	10.0	1.0	150	Trace	0.31	Negative	263	8	271	6	64.8	
11	22	46.1	30	11.5	1.3	180	Slight	....	Negative						
12	23	45.5	3.3	1.8	0.2	20	Trace	....	Negative						
13	24	44.4	...	14.9	10.6	160	Negative	0.26	Negative	257	24	281	6	61.7	
14	25	44.3	...	22.3	15.9	240	Negative	....	Negative						
15	26	44.4	10	3.8	0.4	60	Negative	0.22	Negative	318	24	332	7	56.2	
16	27	44.0	20	8.6	0.9	125	Negative	....	Negative						
17	28	44.2	30	11.3	1.4	180	Trace	....	Negative						
18	29	44.0	10.3	26.3	16.3	300	Trace	....	Negative						
19	30	43.0		Fast			Negative	....	Negative						
20	31	43.0	...	50.0	64.4	805	Negative	....	Negative						
21	32	43.6	...	50.0	64.4	805	Negative	0.25	Negative	.....	.....	.....	.....	58.3	

is demonstrated and must be considered in the future feeding and observation of the patient.

GROUP 1.—Case 2234, patient aged 54 years, diabetic for five years, emaciation and clinical symptoms of moderate severity, but mild in ability to tolerate a sufficient diet for maintenance.

The table shows no tendency to acidosis during the period of preliminary observation (January 25 and 26) or during the fasting period (January 28 to 31). The subsequent carbohydrate tolerance test (February 1 to 16) shows a tolerance of at least 150 gm. of carbohydrate when given in the form of green vegetables alone. At this point the patient refused further hospital treatment, but subsequently he tolerated a maintenance diet of 40 calories per kg. body weight, including 30 gm. carbohydrate and 1.5 gm. protein per kg. body weight (From Jan. 25 to Feb. 16, 1916).

GROUP 2.—Case 2686, patient aged 13 years, diabetic one year, extreme in acid intoxication. The patient was admitted on the verge of coma, being so stuporous that it was impossible to attract his attention by any means. The combining power of the blood for CO_2 (12.2 volume per cent.) agreed with the clinical picture in indicating extreme acidosis. Therefore, the usual preliminary observation period was omitted. Fasting was immediately instituted, and sodium bicarbonate given by mouth (together with the other therapeutic measures described in the text). Within twenty-four hours the CO_2 combining power of the plasma had risen to 26.8 volume per cent., and there was a corresponding improvement in the clinical condition of the patient, consciousness having completely returned and signs of coma having disappeared. After five days fast the plasma CO_2 was nearly normal for a child 13 years of age; the patient was alert and apparently in as good condition as could be expected in a normal child after such a fast. The fast was continued for four days more, however, until the patient became aglycosuric.

The subsequent carbohydrate tolerance test showed a tolerance of 90 gm. of carbohydrate when given in the form of green vegetables alone, and a maintenance diet of 40 calories per kg. body weight including 30 gm. of carbohydrate and 2 gm. of protein per kg. was tolerated without glycosuria or acidosis.

A year and a half after admission word was received that the patient had died in coma following a break in diet. (From February 22 to March 28, 1916.)

GROUP 3.—Case 2480, aged 27. Diabetic four years, severe in carbohydrate intolerance and in a continuous low grade acid intoxication despite dietetic treatment. The summary shows a low grade acidosis during the preliminary observation diet (October 15 and 16) and during the subsequent fasting period (October 17 to 25). During the carbohydrate tolerance test (October 25 to November 6) the plasma bicarbonate barely rose above the minimum normal (53 volume per cent. CO_2), never approaching the average normal (65 volume per cent.), and on the maintenance diet (November 8 to 10) it again fell just below 53. (From October 15 to Nov. 10, 1915.)

GROUP 4.—Case 2414, patient aged 17 years, diabetic one year, was severe in carbohydrate intolerance, and admitted with a dangerous degree of acidosis (plasma CO_2 26.4 volume per cent.). The patient fasted for seven days before admission, following, he thought, the technic employed in this hospital, which he had experienced on two previous admissions.

The summary shows a case in severe acid intoxication (plasma CO_2 26.4 volume per cent.) on admission to the hospital, after a fast of seven days at home. The fast was continued for another day under hospital observation. This was followed by a further drop in the plasma CO_2 of 2.2 volume per cent., which, at this low level, with the onset of hyperpnea and his history of fasting at home, was taken as indication enough to interrupt the fast. The second day in the hospital the patient was put on a diet of lean meat and eggs, constituting 19 calories per kg. body weight. This was accompanied by

sodium bicarbonate by mouth. The following morning the hyperpnea had vanished and the plasma CO_2 had risen to 34.3 per cent. The diet was gradually cut down during the next ten days and the bicarbonate therapy continued until the patient had a normal plasma CO_2. The subsequent fast of five days made the patient aglycosuric and cleared up the ketonuria (Gerhardt reaction).

A carbohydrate tolerance test was given after the fasting period. This was so low (only 30 gm. of carbohydrate when green vegetables alone were given) that a second carbohydrate tolerance test was attempted, as it was thought probable that the severe acidosis present on admission had in some way mitigated against a higher tolerance. The second test confirmed the first.

The maintenance diet was then gradually built up to 1,550 calories (39 calories per kg. body weight), which included 2 gm. of protein per kg. body weight. No carbohydrate was tolerated on mixed diet.

The patient died a year later (March, 1917) in coma. (From February 19 to March 21, 1916.)

Individual diabetics vary greatly, not only in their ability to metabolize food without glycosuria, but also in their tendency to develop acidosis. Fasting decreases this tendency in most patients, but greatly exacerbates it in a minority. It has been found that it is possible to divide diabetic patients into four groups, according to their tendencies to develop acidosis, and that more or less typical treatment is required for the members of each group.

In this paper are described the methods employed at the hospital of the Rockefeller Institute to detect as early as possible the development of acidosis and to prevent its progress and typical examples are given of the procedure and results with patients of each group.

SINO-ATRIAL HEART BLOCK IN A CHILD

WITH OBSERVATIONS ON THE EFFECTS OF ATROPIN AND VAGUS STIMULATION *

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The cardiac arrhythmias of childhood are largely confined to those alterations in rhythm which are governed by the rate of stimulus production in the sino-atrial node. This function is stimulated or depressed by the influence of extracardiac nerves, the vagus and the sympathetic, which in the young are especially active. Of the arrhythmias arising in the sino-atrial node, the simple respiratory arrhythmia which characterizes Mackenzie's "youthful heart" is the most common. There is another type of sinus arrhythmia which is independent of the respiration, but which still has a peculiar phasic character. The cardiac cycles increase progressively in length until the rate is notably retarded. then become shorter until the more rapid rhythm is again established. The rhythm of the sinus node may be interrupted by excitation waves arising at some lower point in the primitive cardiac tissue and retrograde stimulation disturb the fundamental rhythm, or the focus of stimulus production may be shifted within the node from one group of cells to another possessing a different inherent rate of impulse production. The function of pacemaker may also be temporarily assumed by specialized tissues elsewhere in the heart, often in the atrial wall or in the atrioventricular node, which, if possessed of a rapid rate of impulse production, will result in a paroxysmal tachycardia or an atrial flutter.

It is known from experimental and clinical evidence that many of these variations in rhythm may be produced by direct or indirect stimulation of the vagus or of the vagus center. The cardiac response of hypervagotonic individuals to reflex stimulation is characterized by marked changes in the pulse rate. Fear, anger, hunger, deepened respiration, the act of swallowing or defecation are accompanied by transient arrhythmia. Direct stimulation by pressure on the vagus, especially that of the right side, will retard the production of excitation waves at the sinus node in hearts susceptible to vagus influence. The oculocardiac reflex, elicited by pressure over the eyeballs, will also cause a retardation of the pulse rate and a lengthening of the cardiac cycle. Susceptibility to vagal influence is often marked during convalescence from fevers. At such times the response to vagal

* From the Pediatric and Medical Clinics of the Johns Hopkins Hospital.

stimulation by a slowing of the pulse and a slight arrhythmia is considered by Mackenzie to be evidence of improvement in myocardial tone. In all these conditions there is a delicate balance between the influences of the sympathetic and the vagus. When this balance is disturbed the rate of impulse production varies from beat to beat and a true sinus arrhythmia exists.

It is customary to classify interferences with impulse conduction according to the locality of the obstruction as determined by the interpretation of the electrocardiographic or polygraphic record. The most common example, that to which the term "heart block" is generally applied, consists of a defect in the mechanism of impulse conduction between the atrium and the ventricle. The excitation wave may, however, be interrupted at any point in its course. If the impulse is blocked in the sino-atrial node, the atrioventricular node or in the bundle of His, where only one path is available, the result is a "dropped beat." In other areas an excitation wave blocked in its normal path will traverse an unusual route, and the electrocardiographic picture gives evidence of the irregular course of such an impulse. Sino-atrial block is due to a structural or functional defect or to some neurogenic influence that effectively blocks an excitation wave within the sinus node or between the node and the atrial musculature. There is, therefore, no evidence of atrial activity, and the whole heart comes to a standstill for a period of one or more cardiac cycles. Measurement of graphic records show that in sino-atrial block a regular rhythm underlies the apparent arrhythmia. This fundamental rhythm is maintained at some focus within the sino-atrial node and is represented by atrial contractions whenever excitation waves are released. Each interruption is, therefore, approximately equal to two or more cardiac cycles of normal duration. Sinus arrhythmia of a respiratory or phasic type may complicate a sinus block and at times still further modify the rhythm.

Both complete and partial sino-atrial block have been produced experimentally in animals. By gradual isolation of the sinus node in dogs and by clamping lower portions of the node, Eyster and Meek[1] have been able to reproduce and demonstrate, under electrocardiographic control, the rhythm which characterizes sino-atrial block in man. That which they secured as a result of these manipulations was a functional block due to artificial structural defects, a condition comparable to that usually found in atrioventricular block. Sino-atrial block is sometimes associated with the administration of digitalis. Ten out of eighteen cases collected by Levine[2] were, at the time of

1. Eyster, J. A. E., and Meek, W. J.: Arch. Int. Med. **19**:117 (Jan.) 1917.
2. Levine, S. A.: Arch. Int. Med. **17**:153 (Feb.) 1916.

observation, under digitalis. White[3] and Parkinson[4] report cases in which this form of block was present only during the periods of digitalis administration. Cushny[5] has produced a two-to-one sino-atrial block with aconitine. Eyster and Meek[6] and Cohn[7] have shown that the condition will follow the administration of morphin in large doses.

Sino-atrial block is not a common clinical finding. Of 2,000 electrocardiographic records taken in the Johns Hopkins Hospital only four show this type of arrhythmia. The condition has been clinically studied by Levine[2] who collected the fourteen cases reported in the medical literature and added to this series four which have come under his own observation. The youngest patient whose case is reported is one seen by Joachim.[8] The patient was a boy, aged 15, with a previous history of rheumatism, mitral insufficiency and acute pericarditis. The only graphic records obtained were from the radial artery. Wilson,[9] in reviewing the circulatory disturbances of childhood, calls attention to the fact that up to that time (1915) no cases of sino-atrial block in childhood had been reported.

The case here presented is one of sino-atrial heart block occurring in a boy, aged 11 years, a patient from the Harriet Lane Hospital in the service of Dr. John Howland, who has kindly furnished the clinical data for this report.

CLINICAL REPORT

H. N., a boy, aged 11, was admitted to the hospital June 26, 1917. He is the younger of two children. The mother is of a nervous temperament. The father had rheumatic fever five years ago.

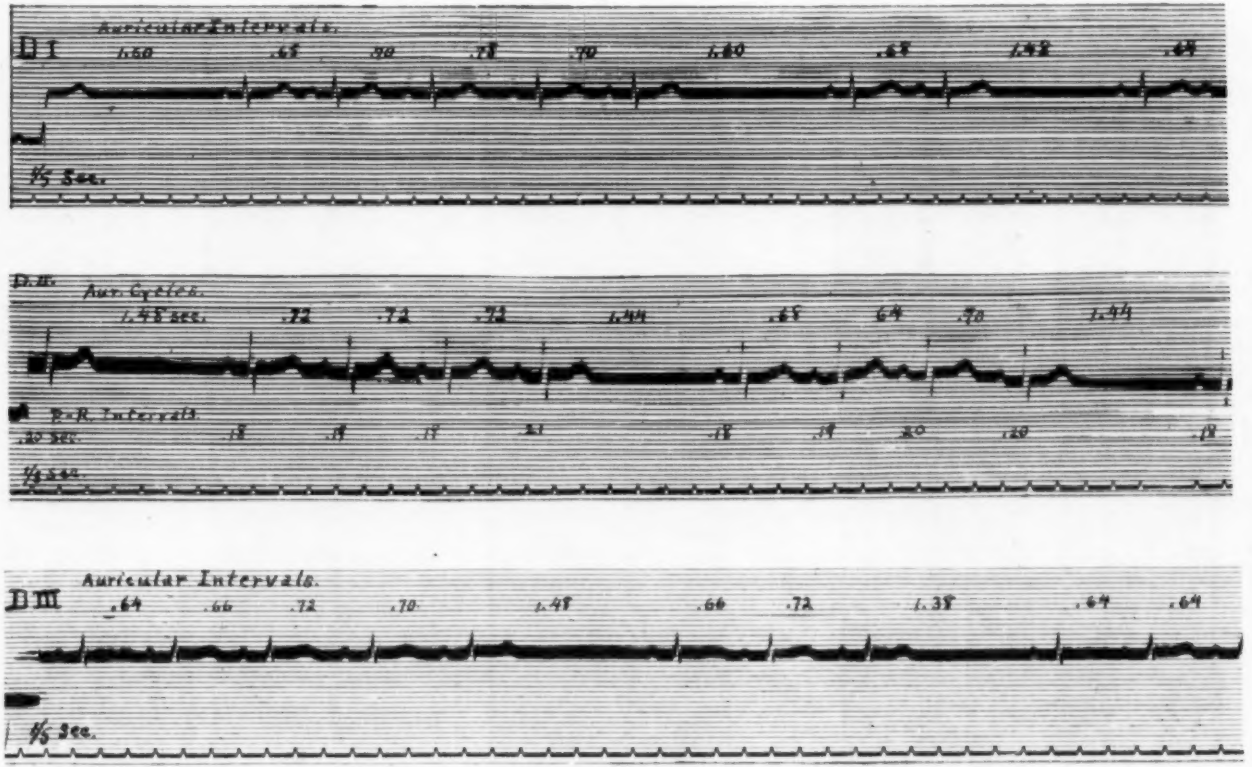
Past History.—During infancy the patient had frequent digestive disturbances. Breast feeding was supplemented from the age of six months by various milk modifications. Dentition began at six months. He walked when one year of age and began to talk at the age of 15 months. He is now in the fourth grade at school.

In early childhood he had measles and chickenpox; no mumps, scarlet fever or chorea. He caught cold easily, and frequently had sore throat with fever. The mother states that when the boy was 2 years old she was told that he had a weak heart. His playing was often interrupted because of shortness of breath.

One month ago he was sick with sore throat, headache, fever and vomiting. There was no eruption. He returned to school but complained of headache and pains in the arms. June 19 prostration was marked. He was feverish and the headache increased. The following day his right hip and left ankle became painful. Since then both ankles have alternately been painful and swollen.

Present Illness.—On admission his temperature was 101.6 F., pulse 88, respiration 24. His general appearance was that of a rather delicate child, small for his age, resting comfortably in bed and complaining of pain only

3. White, P. D.: Boston M. & S. J. **175**:233 (Aug. 17) 1916.
4. Parkinson, J.: Heart **6**:335, 1917.
5. Cushny, A. R.: Heart **1**:1, 1910.
6. Eyster, J. A. E., and Meek, W. J.: Heart **5**:137, 1914.
7. Cohn, A. E.: J. Exper. Med. **18**:715, 1913.
8. Joachim, G.: Deutsch. Arch. f. klin. med. **85**:373, 1905.
9. Wilson, F. N.: Am. J. Dis. Child. **10**:376 (Oct.) 1915.



Figs. 1, 2 and 3.—Derivations I, II and III. June 30, 1917. Sino-atrial block. Atrial cycles are measured from P to P. One cm. deflection equals 1 millivolt. Time recorded in fifths of a second.

when moved. He answered questions and cooperated intelligently. On examination the cervical glands were found somewhat enlarged, the inguinal lymph nodes small but palpable. The teeth were in poor condition; there was pyorrhea; the gums bled easily. Both tonsils were markedly enlarged, red and ragged, but without follicular exudate. The lungs were negative. Cardiac dulness was increased to the right. The apical impulse was in the fifth interspace, three and three-fourth inches from the midsternal line. On auscultation the first aortic sound was weak; the second aortic sound was clear, the second pul-

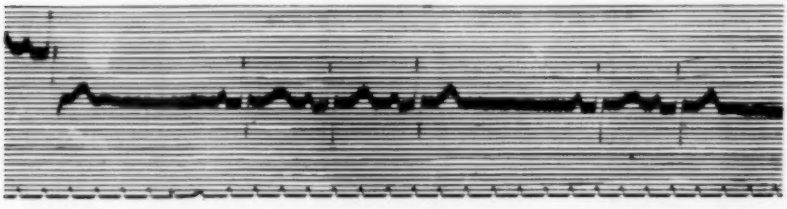


Fig 4.—Derivation II. July 3, 1917. Atropin observation. Control. Sino-atrial block. Ventricular rate 64.

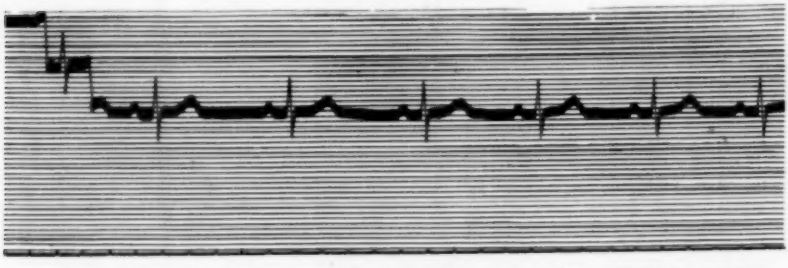


Fig. 5.—Ten minutes after hypodermic administration of 1/150 grain of atropin. No block. Slight sinus arrhythmia. Rate 68.

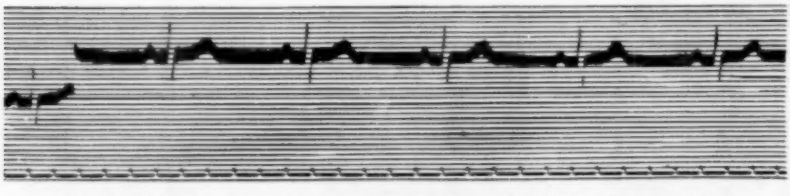


Fig. 6.—Twenty-three minutes after atropin. No block. Regular rhythm. Rate 58.

monic sound was rough and accentuated. A soft, blowing murmur was heard over the precordium but was only faintly transmitted beyond the apex. Occasional "dropped beats" were noted. The liver was not enlarged; the spleen was not palpable. There was slight tenderness in the region of the left shoulder; the left ankle was swollen, reddened and tender. Other joints were negative. Reflexes normal. The urine showed albumin in small quantities but there were no pus cells, casts or red blood cells, no sugar and no acetone. The von Pirquet reaction was negative. The white blood count was 18,400.

On admission sodium salicylate and sodium bicarbonate were prescribed in suitable doses. No digitalis was administered.

Clinical Course.—June 27, 1917: Pain in ankle subsided. Patient's condition improved; no change in heart findings. Temperature 100 F.

June 30: An electrocardiographic examination was made.

July 2: Cardiac dulness extends only three inches from the midsternal line. The systolic murmur is the same. The second pulmonic sound is sometimes reduplicated. Temperature 99 F.; pulse during sleep is 50 and fairly regular.

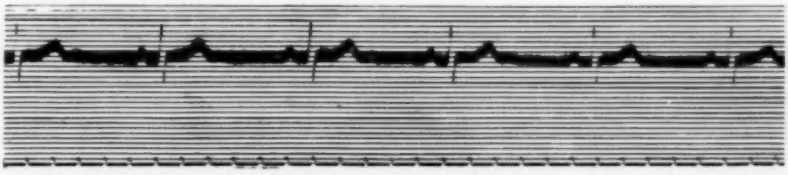


Fig. 7.—Thirty minutes after atropin. No block. Regular rhythm. Rate 55.

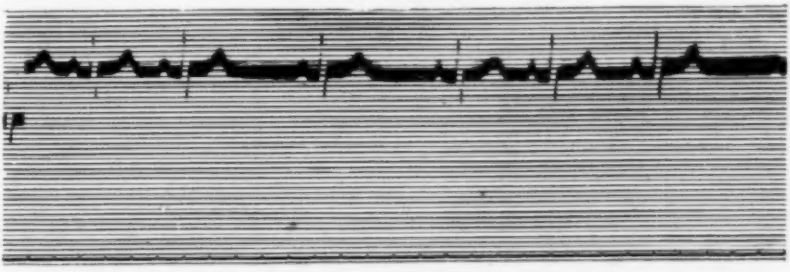


Fig. 8.—Forty-three minutes after atropin. Sinus arrhythmia. Rate 68.

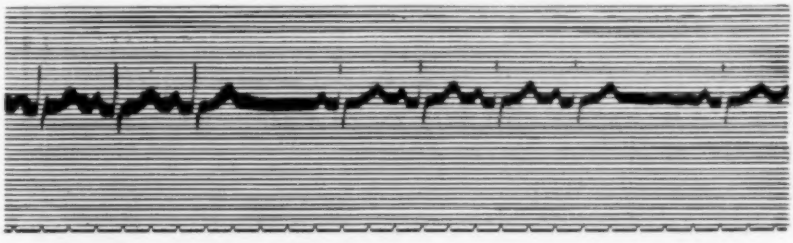


Fig. 9.—Fifty-five minutes after atropin. Sino-atrial block returns.

July 3: An electrocardiographic examination was made. Atropin, 1/150 grain, was administered.

July 4: The patient had gastrointestinal disturbances, and his pulse was very irregular.

July 5: The pulse was irregular, with pauses of different lengths. The rate was about 48.

July 9: An electrocardiographic examination was made and atropin, 1/100 grain, was administered.

July 11: An electrocardiographic examination was made.

July 13: Final note. The general condition of the patient was good. The apical impulse was two and three-fours inches from the midsternal line. The pulse was irregular, about 60 per minute. The temperature was normal. The patient was discharged improved.

Feb. 15, 1918: The patient returned for examination. He has been attending school. His general health was good. There was no recurrence of any pains, but there was slight shortness of breath on exertion. The apical impulse was well within the mammary line. The systolic murmur at the apex was not transmitted to the axilla. The pulse showed the same type of arrhythmia as on previous examinations. An electrocardiographic examination was made. Atropin, 1/75 grain, was administered.

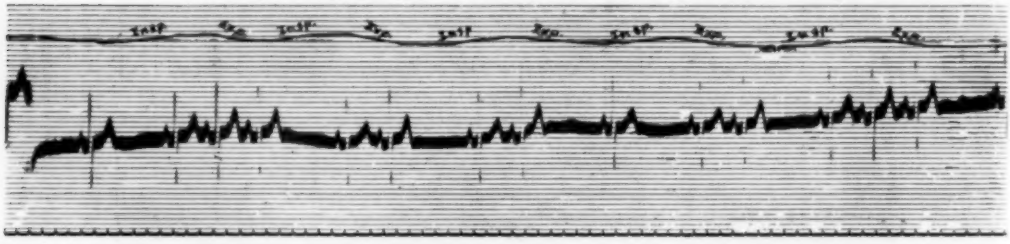


Fig. 10.—Derivation II. July 9, 1917. Control with respiratory curve. Sino-atrial block. Slow film.

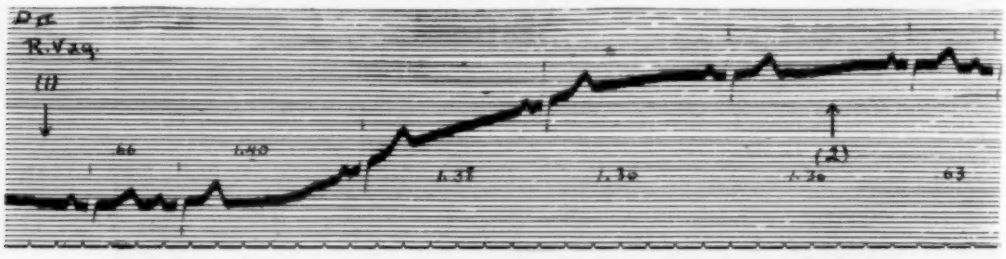


Fig. 11.—Before atropin. Pressure on right vagus. Applied at (1), released at (2). Block is increased.

Electrocardiographic Study

June 30, 1917.—The principal waves of the electrocardiogram (Figs. 1, 2 and 3) are normal for a child of this age. The R waves are low in all three leads; the S deflection is prominent in the first and second leads. P waves are normal. T is upright in all leads. The sequence is normal. Conduction time is slightly prolonged and measures from 0.18 to 0.21 second. Arrhythmia of an unusual type is present in which the normal rhythm is interrupted by frequent pauses approximately equal to two normal cycles. There is no evidence of auricular activity during these intermissions. The P-R interval is slightly longer in the cycles just preceding the pause. Measurement of the individual atrial cycles (P-P) shows that the atrial intervals preceding the intermissions are usually longer than those which immediately follow them. The long cycles are either equal to, or slightly longer than, the period occupied by two short cycles. The short atrial cycles which represent the fundamental sinus rhythm measure

on the average 0.67 second, indicating a production rate of 90 or 92 excitation waves per minute. The long pauses average 1.45 seconds. The diagnosis is sino-atrial block.

July 3, 1917. Controls were taken which showed (Fig. 4) the same arrhythmia as on June 30. There are frequent pauses equal to two or four normal beats. The average length of the normal cycle is 0.65 second; the average length of the pause is 1.4 seconds. The fundamental rate of sinus is 92. The ventricular rate is 64. Atropin, 1/150 grain, was given hypodermically.

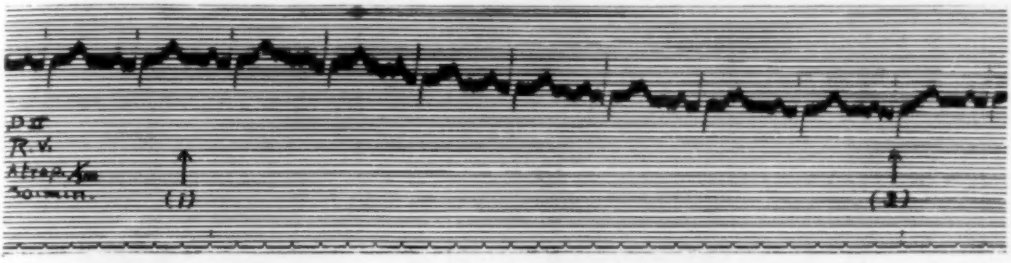


Fig 12.—Before atropin. Pressure on left vagus. Applied at (1), released at (2). No appreciable effect on rhpthm.

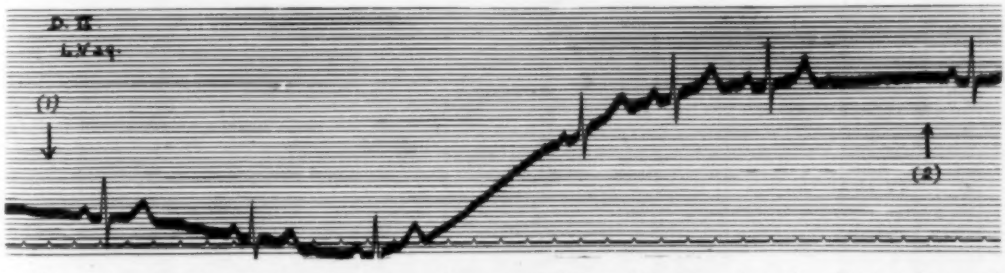


Fig. 13.—Before atropin. Oculocardiac reflex. Pressure applied at (1), released at (2). Block is increased.

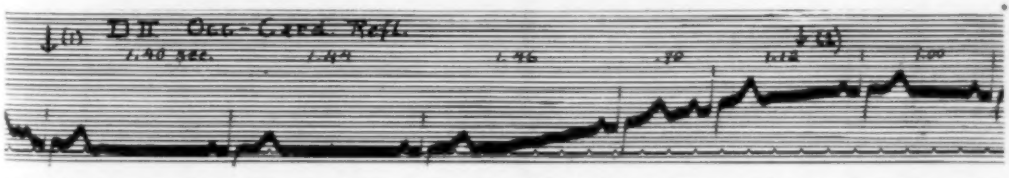


Fig. 14.—After atropin. Pressure on right vagus. Applied at (1), released at (2). No change in rhythm.

Ten minutes after atropin was given the sinus block disappeared (Fig. 5), but a slight sinus arrhythmia persisted. The cardiac cycles measured from 0.70 to 0.98 second. The rate was 68; the P-R interval was 0.18 second.

Twenty-three minutes after atropin was given the rhythm (Fig. 6) was regular; the rate was 58; the cardiac cycles measured 1.02 to 1.08 seconds; the P-R interval was 0.18 second.

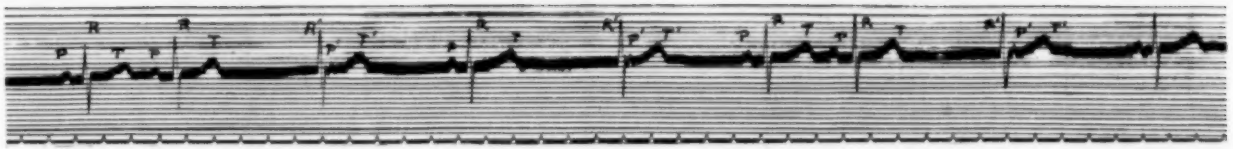


Fig. 15.—Derivation II. July 11, 1917. Sino-atrial block. During the long three-cycle intermissions nodal extra-systoles appear (R'P'T').

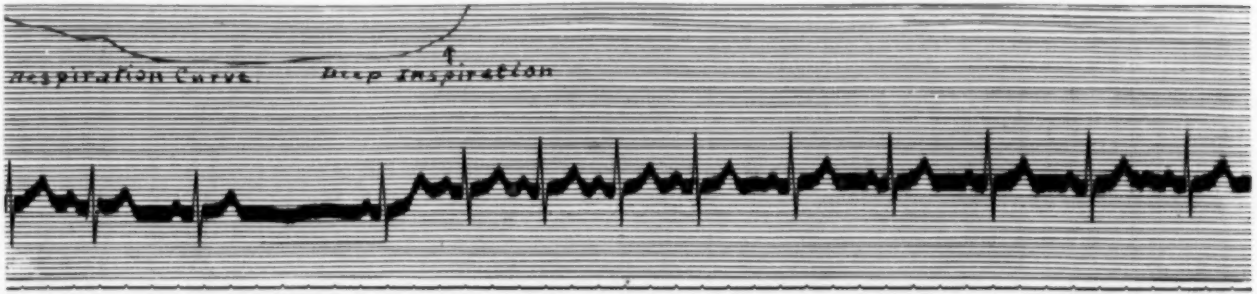


Fig. 16.—Derivation II. Feb. 15, 1918. Sinus block disappears while breath is held in full inspiration. Sinus rate is retarded.

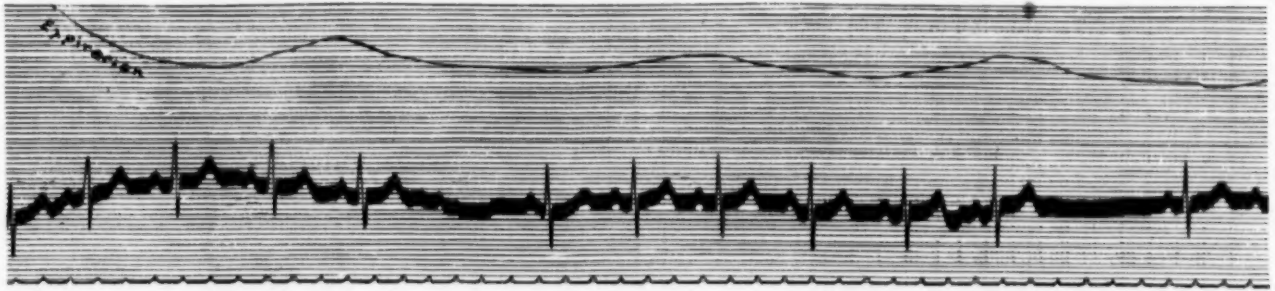


Fig 17.—Continuation of record shown in Fig. 16. There is an intermission of twelve seconds between Figs. 16 and 17. On expiration the characteristic sinus block returns.

Thirty minutes after atropin was given the rhythm was regular (Fig. 7); the rate was 55; the cardiac cycles measured 1.08 seconds; the P-R interval was 0.17 second.

Forty-three minutes after atropin was given there was (Fig. 8) slight sinus arrhythmia; the rate was 68; the cardiac cycles measured 0.71 to 1.06 seconds.

Fifty-five minutes after atropin was given the sino-atrial block (Fig. 9) had returned. There were pauses after three to six normal cycles. The short cycles measured 0.56 to 0.60 second; the pauses measured 1.12 to 1.24 seconds.

July 9, 1917. Controls show sinus block as before (Fig. 10). The short cycles measure 0.60 to 0.66 second; the pauses measure 1.32 to 1.40 seconds. The ventricular rate is 60. The P-R interval is from 0.17 to 0.19 second. A respiratory curve taken with the electrocardiogram shows the relation of the respiration to the arrhythmia. The long pauses occur usually, but not always, during the inspiratory phase. On holding the breath the block entirely disappears, the rate is 57 per minute. Pressure on the right vagus increases the block and eliminates the short cycles; four blocks occur in succession. Pressure on the left vagus produces no appreciable change (Fig. 11). Firm ocular pressure definitely increases the number of blocked impulses (Fig. 12). Atropin, $\frac{1}{100}$ grain, was given hypodermically. Ten minutes afterward there was no block. Sinus arrhythmia was present with cycles measuring from 0.63 to 1.15 seconds; the ventricular rate was 66. Sixteen minutes after the injection of the atropin the rhythm was regular. Twenty-two minutes after the injection the rhythm was regular, the rate was 73 and the cardiac cycles measured from 0.72 to 0.88 second.

Twenty-six minutes after atropin injection the rate was 82. Pressure at this time on the right vagus produced no effect (Fig. 13). Deep pressure on the eyeballs produced a brief return of the sinus block showing that the vagus was still partially active. Sixty minutes after atropin was given the sinus block type of arrhythmia returned; the fundamental rhythm became more rapid; the short cycles measured from 0.56 to 0.60 second; the pauses measured from 1.08 to 1.14 seconds; the ventricular rate was 68.

July 11, 1917. A sino-atrial block was present, but electrocardiograms also showed frequent nodal extrasystoles (Fig. 14). The short cycles measure 0.64 to 0.68 second. After one or two normal beats there is an interval of from 2.22 to 2.30 seconds before another normal excitation wave appears. This interval is greater than those previously found and is approximately equal to the period occupied by three normal cycles. In the middle of this interval there appears, each time, a nodal extrasystole. The atrium and ventricle contract simultaneously; a small diphasic P wave appears between the R and the T_1 following the R wave by 0.08 second. The extrasystole is always the same distance, 1.12 to 1.16 seconds from the preceding R wave. The ventricular rate is 58. Holding the breath in full inspiration eliminates the extrasystoles and the arrhythmia. While the breath is held the cardiac cycles measure from 0.78 to 0.86 second with a ventricular rate of 80.

Feb. 15, 1918. Electrocardiograms show sino-atrial block of the same type as existed in July, 1917. The short cycles are somewhat more numerous. No extrasystoles were found. Right vagus and ocular pressure, as on former occasions, produced an increase in the number of dropper beats. The arrhythmia again disappeared when the breath was held in full inspiration (Figs. 15 and 16). Atropin, $\frac{1}{75}$ grain, was given hypodermically. Five minutes later the arrhythmia was still present. In ten minutes it had disappeared; the rate was 80. Twenty minutes after atropin administration the rate had increased to 115. One hour later it was 120, the rhythm still being regular. Two hours after the atropin injection the heart had resumed its characteristic arrhythmia.

DISCUSSION

The arrhythmia found in this case is that usually referred to as "sino-auricular block." There is a complete standstill of the entire

heart for one or more beats, the intermissions being separated by one to six normal cardiac cycles. The blocks which characterize the records from this patient may hypothetically result from a failure of the sino-atrial node to generate an excitation wave, from a failure of the atrial musculature to respond to the excitation or from interference with the impulse in its passage to the atrium. The persistence of a fundamental rhythm underlying this arrhythmia is evidence of the maintenance of rhythmic impulse production. There is no evidence of diminished atrial excitability and the atrium responds to every excitation wave when the rate is much augmented.

The arrhythmia is best explained by the existence of some factor which interferes with the transmission of correctly timed excitation waves. Such a functional defect may be dependent either on structural changes or the influence of depressor nerves. The sino-atrial block produced experimentally by Eyster and Meek[1] is essentially a functional block due to structural changes. Our records from this case present some of the same characteristics. After several normal contractions an impulse fails to pass. In the series of normal beats the atrial cycles preceding an intermission are slightly longer than those which follow it, suggesting an increasing delay in impulse transmission prior to the appearance of the block. Such an observation was used by Levine[2] as a basis for the hypothesis that sinus arrhythmias associated with sino-atrial block are due to a progressive delay in impulse transmission. Were this hypothesis applicable in the explanation of this arrhythmia, a retardation in the rate of impulse production would eliminate, and an acceleration would increase, the block. The rate was reduced and the block eliminated in this case by holding the breath after deep inspiration, but when stronger vagus stimulation was employed, directly by pressure on the right vagus, or indirectly by ocular pressure, the intermissions increased in frequency. The administration of $\frac{1}{75}$ grain of atropin increased the rate to 120 per minute, but with the acceleration the blocks disappeared. It is evident that if there be in this case any structural defect, it is a minor factor, and that the abnormal rhythm is due chiefly to vagus influence. The electrocardiograms taken on July 11 (Fig. 14) in which there occur three cycle pauses broken by a nodal extrasystole, bear a striking resemblance to those taken by Cohn[7] after the administration of morphin to "right vagus dogs," those in which the left vagus had been severed.

It is known that structures in various parts of the heart have the power, under certain conditions, of initiating excitation waves, and that these areas have different rates of impulse production. Meek and Eyster[10] have shown that even within the sino-atrial node the

10. Meek, W. J., and Eyster, J. A. E.: Am. J. Physiol. **34**:368, 1914.

location of the pacemaker may be changed by moderate vagus stimulation. It is possible that different portions of the node have different rates of stimulus production, and that by a shifting of the pacemaker within the node the rhythm is changed. Macleod[11] suggests that varying degrees of vagus stimulation may have a selective action on the strength, rate, impulse transmission and excitability of the heart muscle. Varying the degree of vagus paralysis in a hypervagotonic individual would inversely modify the strength of vagal stimulation.

The primary action of atropin is to stimulate the vagus center in common with other medullary centers. A preliminary slowing of the pulse is sometimes observed, but this is quickly replaced by the tachycardia which accompanies the atropin action on the vagus endings. To modify the action of the vagus, atropin was given hypodermically. A small dose, $\frac{1}{150}$ grain, produced a slowing of the pulse and an elimination of the arrhythmia. This effect appeared in ten minutes and persisted for almost an hour without the acceleration which usually follows atropin administration. On another occasion the same result followed the injection of $\frac{1}{100}$ grain of atropin. The arrhythmia disappeared and a regular rhythm, slower than the fundamental rhythm, was maintained for an hour. The administration of $\frac{1}{75}$ grain produced a rapid increase in the rate of the heart to thirty beats above the fundamental rhythm. The arrhythmia was eliminated. The larger dose produced a simple tachycardia, the usual result of atropin administration. Wilson[12] concludes, from observations on patients in whom he produces a temporary atrioventricular rhythm, that there is a selective action of atropin by which the vagus terminations in the atrioventricular node are affected before those in the sinus node. In a similar manner it appears that in the instance here recorded atropin acts first on the vagus terminations in and about the sinus node which control conductivity and later on those which control the rate of impulse production.

A prominent feature of these electrocardiograms is the persistence under normal conditions of a fundamental sinus rhythm. The portion of the sinus node which acts as pacemaker has, it is evident, a rate of stimulus production which results in the formation of excitation waves at the rate of 90 per minute. This has been referred to as the fundamental rhythm. The demands of the circulation only call for 58 to 66 ventricular contractions per minute. The adjustment of the sinus rate to the circulatory demand is largely dependent upon the balance established between the opposing influences of the vagus and the sympathetic nerves. While occasionally this heart shows beats of intermediate

11. Macleod, J. J.: Physiology and Biochemistry in Modern Medicine, 1918, p. 227.
12. Wilson, F. N.: Arch. Int. Med. **16**:989 (Dec.) 1915.

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length, nearly all cardiac cycles fall into two groups; those which measure approximately 0.66 seconds, a rate of 90 per minute, and those which occupy 1.20 to 1.40 seconds. The pacemaker is adjusted to the 90 per minute rate, and the vagus, instead of depressing stimulus production and thereby reducing the rate, affects first the conductivity and produces a sufficient number of intermissions to bring the rate to about 60 contractions per minute, the number required to properly maintain the circulation. In Figure 14 is shown a block of three cycles. This delay permits a ventricular release, the excitation wave originating in or near the atrioventricular node and resulting in the simultaneous contraction of auricles and ventricles. By means of this nodal extrasystole introduced in each three cycle intermission, the heart maintains the requisite number of contractions per minute.

The action of small doses of atropin in eliminating the arrhythmia without producing sufficient vagal inhibition to permit the acceleration of impulse production, and the persistence of this slow, regular rhythm are of clinical interest. They indicate a prolonged primary atropin effect which moderately stimulates the vagus center and retards impulse production, while coincident with this is a selective peripheral action of atropin on the vagus endings which control impulse transmission, thus facilitating the passage of excitation waves to the atrium.

SUMMARY

A case is reported of a child, 11 years old, with acute arthritis, who presents a typical sino-atrial block. Changes in heart rate and rhythm by vagus stimulation and by the administration of atropin are demonstrated. It is found that atropin in small doses will eliminate the arrhythmia without producing an acceleration of the heart rate. Electrocardiographic records accompany the report and illustrate the observations.

The American Medical Association will pay 50 cents each for the following issues of the Archives of Internal Medicine: January, March, June and August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. Address to AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.